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ANNALS

OF OTOLOGY, RHINOLOGY & LARYNGOLOGY

ANNALS OF HEAD & NECK MEDICINE & SURGERY

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ECTS OF LATERAL MANUAL COMPRESSION UPON GLOTTIC INCOMPETENCE: OBJECTIVE EVALUATIONS

MALIGNANT HYPERTHERMIA IN THE OLARYNGOLOGIC PATIENT: PROSPECTIVE IESTHETIC AND SURGICAL MANAGEMENT OF EIGHT CHILDREN

STAGING FOR CHOLESTEATOMA IN THE CHILD, ADOLESCENT, AND ADULT

NICAL DIAGNOSIS OF ANTERIOR INFERIOR CEREBELLAR ARTERY THROMBOSIS

VENTION OF ASPIRATION IN INFANTS AND UNG CHILDREN: FEDERAL REGULATIONS

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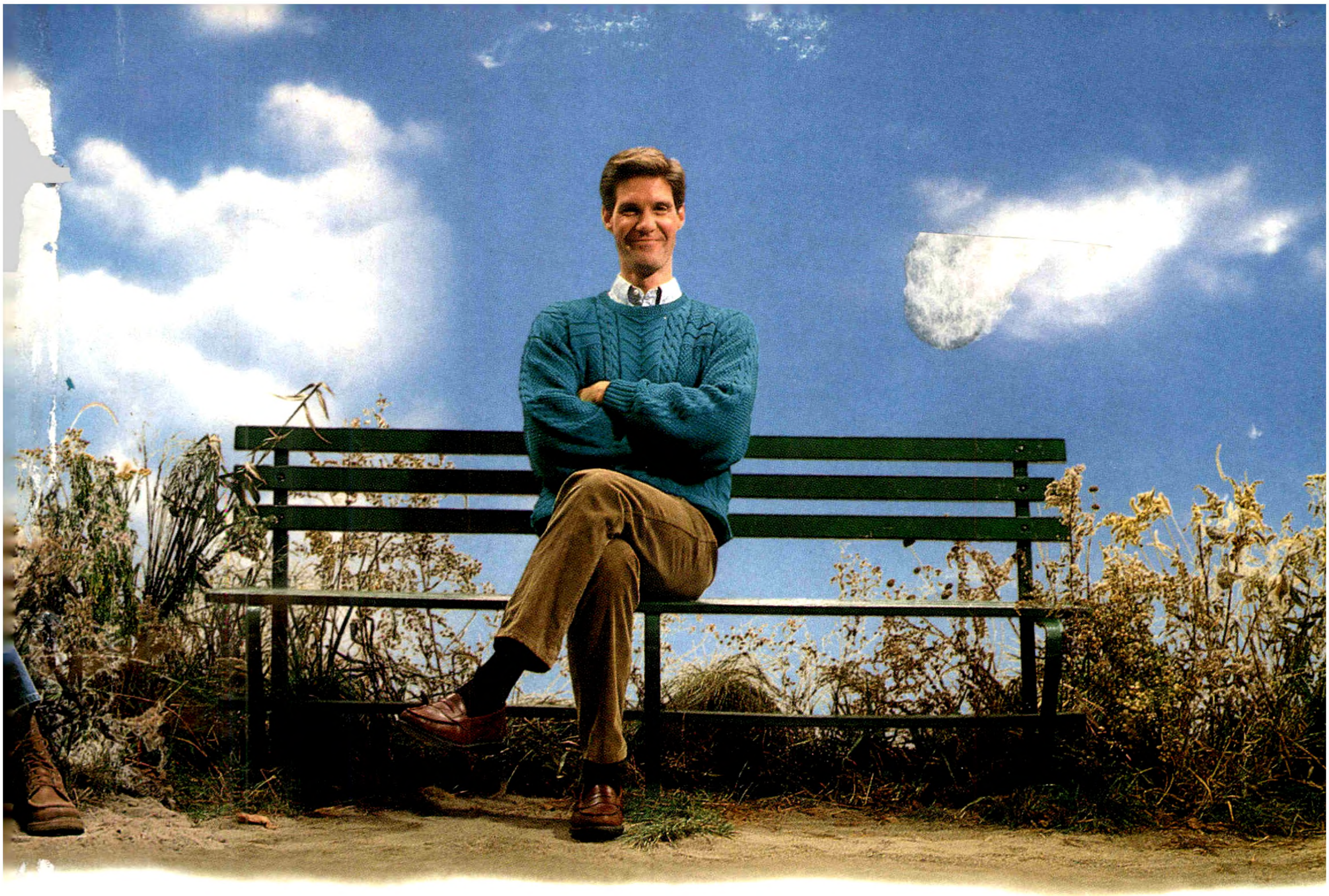

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*In two out of four measures of nasal symptoms, $P < 0.01$.
†See WARNINGS and PRECAUTIONS in Brief Summary of Prescribing Information on next page. ‡Calculated on the dried basis.

Please consult Brief Summary of Prescribing Information on next page.

Beconase® Inhalation Aerosol
(beclomethasone dipropionate, USP)
For Nasal Inhalation Only

BRIEF SUMMARY

Beconase AQ® Nasal Spray, 0.042%*
(beclomethasone dipropionate, monohydrate)
***Calculated on the dried basis. For Intranasal Use Only.**

SHAKE WELL BEFORE USE.

The following is a brief summary only. Before prescribing, see complete prescribing information in Beconase® Inhalation Aerosol and Beconase AQ® Nasal Spray product labeling.

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of either preparation contraindicates its use.

WARNINGS: The replacement of a systemic corticosteroid with Beconase® Inhalation Aerosol or Beconase AQ® Nasal Spray can be accompanied by signs of adrenal insufficiency.

Careful attention must be given when patients previously treated for prolonged periods with systemic corticosteroids are transferred to Beconase Inhalation Aerosol or Beconase AQ Nasal Spray. This is particularly important in those patients who have associated asthma or other clinical conditions where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that the combined administration of alternate-day prednisone systemic treatment and orally inhaled beclomethasone increases the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, Beconase Inhalation Aerosol and Beconase AQ Nasal Spray treatment should be used with caution in patients already on alternate-day prednisone regimens for any disease.

If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, Beconase Inhalation Aerosol and Beconase AQ Nasal Spray should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy.

PRECAUTIONS: General: During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, eg, joint and/or muscular pain, lassitude, and depression.

Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone.

Extremely rare instances of wheezing, nasal septum perforation, and increased intraocular pressure have been reported following the intranasal application of aerosolized corticosteroids. Although these have not been observed in clinical trials with Beconase AQ® Nasal Spray, vigilance should be maintained.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuation of treatment with Beconase® Inhalation Aerosol or Beconase AQ Nasal Spray.

If persistent nasopharyngeal irritation occurs, it may be an indication for stopping Beconase AQ Nasal Spray.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of Beconase Inhalation Aerosol or Beconase AQ Nasal Spray may suppress HPA function.

Beconase Inhalation Aerosol and Beconase AQ Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; untreated fungal, bacterial, or systemic viral infections; or ocular herpes simplex.

For either preparation to be effective in the treatment of nasal polyps, the aerosol or spray must be able to enter the nose. Therefore, treatment of nasal polyps with these preparations should be considered adjunctive therapy to surgical removal and/or the use of other medications that will permit effective penetration of these preparations into the nose. Nasal polyps may recur after any form of treatment.

As with any long-term treatment, patients using Beconase Inhalation Aerosol or Beconase AQ Nasal Spray over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses of Beconase Inhalation Aerosol and Beconase AQ Nasal Spray should be avoided.

Information for Patients: Patients being treated with Beconase Inhalation Aerosol or Beconase AQ Nasal Spray should receive the following information and instructions. This information is intended to aid in the safe and effective use of medication. It is not a disclosure of all possible adverse or intended effects. Patients should use these preparations at regular intervals since their effectiveness depends on their regular use. The patient should take the medication as directed. It is not acutely effective, and the prescribed dosage should not be increased. Instead, nasal vasoconstrictors or oral antihistamines may be needed until the effects of Beconase Inhalation Aerosol or Beconase AQ® (beclomethasone dipropionate, monohydrate) Nasal Spray are fully manifested. One to two weeks may pass before full relief is obtained. The patient should contact the doctor if symptoms do not improve, or if the condition worsens, or if sneezing or nasal irritation occurs. For the proper use of either unit and to attain maximum improvement, the patient should read and follow carefully the patient's instructions section of the package insert.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of rats for a total of 95 weeks, 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have not been performed.

Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrous cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Like other corticoids, parenteral (subcutaneous) beclomethasone dipropionate has been shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately ten times the human dose. In these studies, beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at ten times the human dose or orally at 1,000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Beconase (beclomethasone dipropionate, USP) Inhalation Aerosol or Beconase AQ Nasal Spray is administered to nursing women.

Pediatric Use: Safety and effectiveness in children below 6 years of age have not been established.

ADVERSE REACTIONS: In general, side effects in clinical studies with both preparations have been primarily associated with irritation of the nasal mucous membranes.

Extremely rare instances of wheezing, nasal septum perforation, and increased intraocular pressure have been reported following the intranasal administration of aerosolized corticosteroids (see PRECAUTIONS).

Rare cases of immediate and delayed hypersensitivity reactions, including urticaria, angioedema, rash, and bronchospasm, have been reported following the oral and intranasal inhalation and administration of beclomethasone.

Beconase® Inhalation Aerosol: Adverse reactions reported in controlled clinical trials and long-term open studies are described below. Sensations of irritation and burning in the nose (11 per 100 patients) following the use of Beconase Inhalation Aerosol have been reported. Also, occasional sneezing attacks (10 per 100 adult patients) have occurred immediately following the use of the intranasal inhaler. This symptom may be more common in children. Rhinorrhea may occur occasionally (1 per 100 patients).

Localized infections of the nose and pharynx with *C albicans* have occurred rarely (see PRECAUTIONS).

Transient episodes of epistaxis have been reported in 2 per 100 patients. Ulceration of the nasal mucosa has been reported rarely.

Systemic corticosteroid side effects were not reported during controlled clinical trials. If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, ie, Cushing's syndrome, could occur.

Beconase AQ® Nasal Spray: Adverse reactions reported in controlled clinical trials and open studies are described below.

Mild nasopharyngeal irritation has been reported in up to 24% of patients treated, including occasional sneezing attacks (about 4%) occurring immediately following use of the spray. In patients experiencing these symptoms, none had to discontinue treatment. The incidence of transient irritation and sneezing was approximately the same in the group of patients who received placebo in these studies, implying that these complaints may be related to vehicle components of the formulation.

Fewer than 5 per 100 patients reported headache, nausea, or lightheadedness. Fewer than 3 per 100 patients reported nasal stuffiness, nosebleeds, rhinorrhea, or tearing eyes.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

RB2 1006 March 1989

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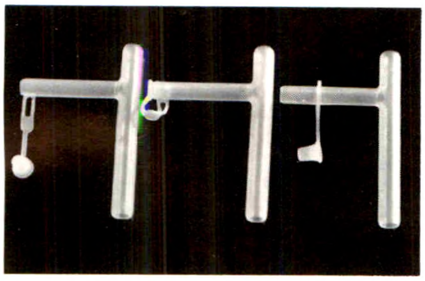

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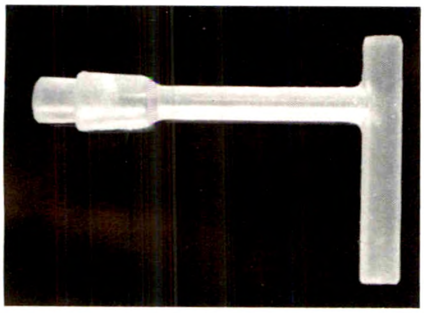

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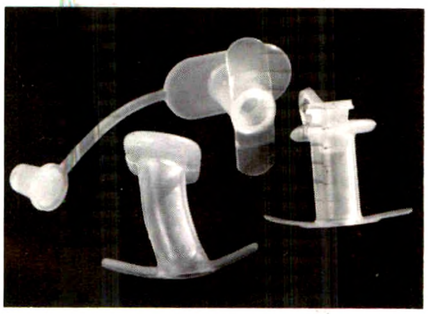

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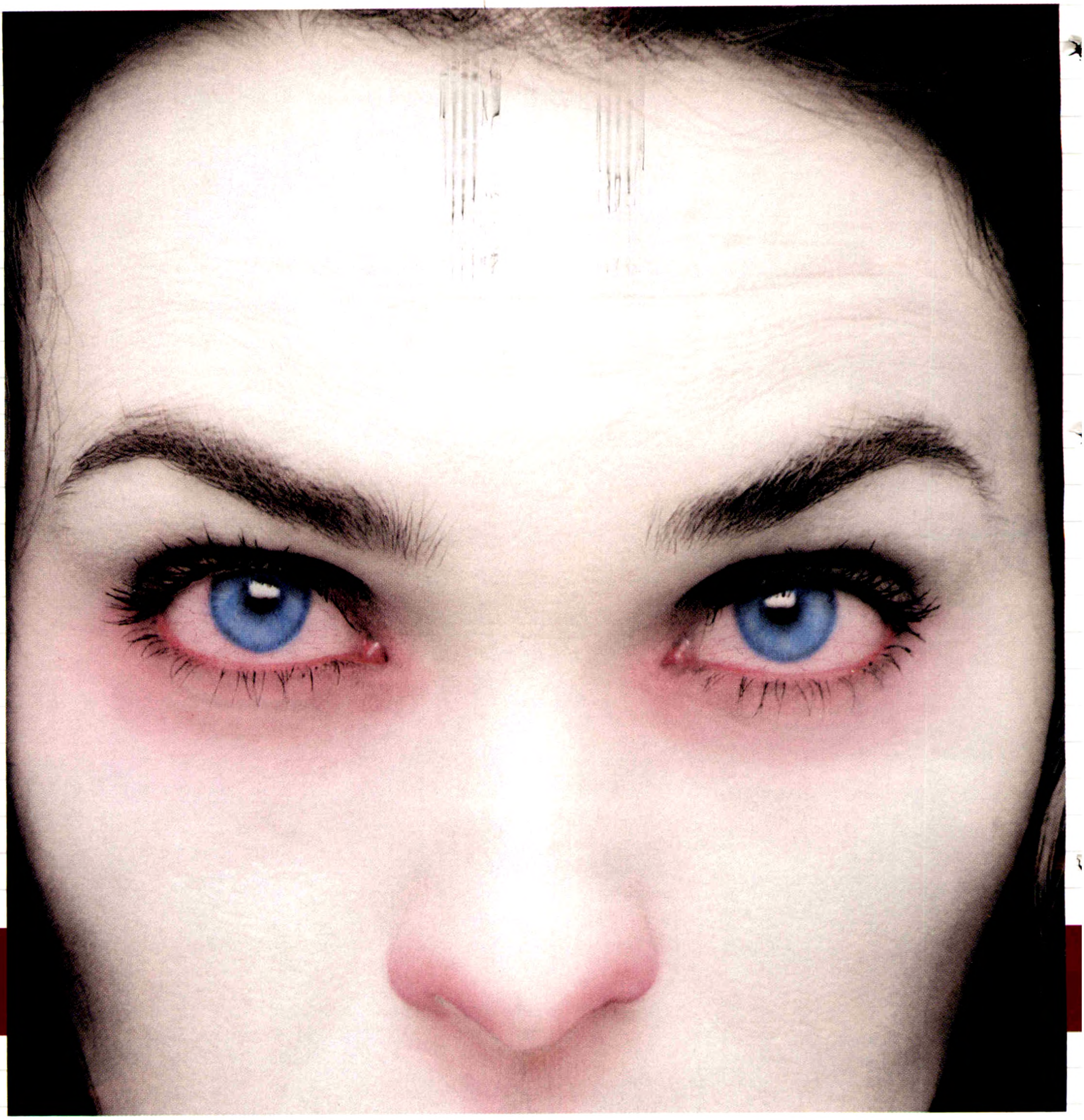

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Please see next page for brief summary of prescribing information.

A PROVEN COMBINATION*

antihistamine/decongestant

TAVIST D®

TABLETS
(clemastine fumarate 1.34 mg, phenylpropanolamine HCl 75 mg extended-release tablets)

BRIEF SUMMARY

TAVIST-D®

(clemastine fumarate, phenylpropanolamine HCl, extended-release tablets) Each tablet contains: clemastine fumarate, 1.34 mg, phenylpropanolamine HCl, 75 mg.

INDICATIONS AND USAGE

Tavist-D® (clemastine fumarate/phenylpropanolamine HCl) Tablets are indicated for the relief of symptoms associated with allergic rhinitis such as sneezing, rhinorrhea, pruritus of the eyes, nose or throat, lacrimation and nasal congestion.

CONTRAINDICATIONS

Tavist-D® (clemastine fumarate/phenylpropanolamine HCl) Tablets are contraindicated in patients hypersensitive to any of the components. Antihistamines should not be used in newborn or premature infants or in nursing mothers. Antihistamines should not be used to treat lower respiratory tract symptoms including asthma. Tavist-D® (clemastine fumarate/phenylpropanolamine HCl) Tablets are contraindicated in patients receiving monoamine oxidase inhibitors (see *PRECAUTIONS — Drug Interactions* in a complete package insert) and in patients with severe hypertension or severe coronary artery disease.

WARNINGS

Antihistamines such as clemastine fumarate should be used with considerable caution in patients with narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, and bladder neck obstruction. Sympathomimetic drugs such as phenylpropanolamine hydrochloride should be used with caution in hypertension, cardiovascular disease, diabetes mellitus, and uncontrolled hyperthyroidism.

Use with CNS Depressants: Antihistamines have additive effects with alcohol and other CNS depressants (hypnotics, sedatives, tranquilizers, etc.).

Use in Activities Requiring Mental Alertness: Patients should be warned about engaging in activities requiring mental alertness such as driving a car or operating appliances, machinery, etc.

Use in the Elderly (approximately 60 years or older): Antihistamines are more likely to cause dizziness, sedation and hypotension in elderly patients. Overdosages of sympathomimetics in this age group may cause hallucinations, convulsions, CNS depression and death in elderly patients.

Use in Children: Safety and effectiveness of Tavist-D® (clemastine fumarate/phenylpropanolamine HCl) have not been established in children under the age of 12. In infants and children, especially, antihistamines in *overdosage* may cause hallucinations, convulsions or death. As in adults, antihistamines may diminish mental alertness, but they may also produce excitation, particularly in young children.

ADVERSE REACTIONS

Antihistaminic Compounds: It should be noted that the following reactions have occurred with one or more antihistamines and, therefore, should be kept in mind when prescribing drugs belonging to this class, including clemastine fumarate. The most frequent adverse reactions reported with clemastine fumarate are underlined.

1. *General:* Urticaria, drug rash, anaphylactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose and throat.
2. *Cardiovascular System:* Hypotension, headache, palpitations, tachycardia, extrasystoles.
3. *Hematologic System:* Hemolytic anemia, thrombocytopenia, agranulocytosis.
4. *Nervous System:* Sedation, sleepiness, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesias, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis, hysteria, neuritis, convulsions.
5. *Gastrointestinal System:* Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.
6. *Genitourinary System:* Urinary frequency, difficult urination, urinary retention, early menses.
7. *Respiratory System:* Thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness.

Sympathomimetic Compounds: *Nervous System* — At higher doses may cause drowsiness, dizziness, nervousness, or sleeplessness, and especially in children may cause excitability. Phenylpropanolamine hydrochloride may cause elevated blood pressure and tachyarrhythmias, especially in hyperthyroid patients.

DOSAGE AND ADMINISTRATION

Adults and children twelve years and over: One tablet swallowed whole every twelve hours.

HOW SUPPLIED

Tavist-D® (clemastine fumarate/phenylpropanolamine HCl, extended-release) Tablets: Containing 1.34 mg clemastine fumarate (equivalent to 1 mg of the free base) and 75 mg phenylpropanolamine hydrochloride. White, round film-coated multiple compressed tablet, embossed "TAVIST-D" on one side and "78-221" on the other. Packages of 100 (NDC 0078-0221-05). TAD-0190-01

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EFFECTS OF LATERAL MANUAL COMPRESSION UPON GLOTTIC INCOMPETENCE: OBJECTIVE EVALUATIONS

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Forceful manual compression of the thyroid and cricoid cartilages modifies the position, shape, and tension of the vocal folds. This is the basis of the four laryngeal manual compression tests, adjunctive examinations used as a means of preoperative assessment of patients for medialization laryngoplasty, ie, Isshiki thyroplasty types I and IV and arytenoid adduction. The laryngeal manual compression tests are simple to perform and noninvasive. Each of the four examinations yields valuable information on the effects on the voice of changes in vocal cord characteristics produced by manual compression. In this report, one of the four tests, lateral manual compression, is evaluated objectively with well-attested methods of videostroboscopic, aerodynamic, and acoustic analysis. The technique of performing lateral manual compression is described, and advantages and disadvantages are noted and compared in 10 patients. Preliminary findings in 4 patients in this group indicate that medialization laryngoplasty should be considered when test results are conclusive of effective glottic closure. Data derived in this preliminary study will be augmented as patients are added to the series.

KEY WORDS — laryngeal framework surgery, laryngeal manual compression tests, medialization laryngoplasty.

INTRODUCTION

Manual compression of the thyroid and cricoid cartilages results in modifications of the position, shape, and tension of the vocal folds. This provides the basis for laryngeal manual compression tests, described by Isshiki et al[1] in 1974 as valuable adjunctive examinations in the preoperative assessment of patients under consideration for laryngeal framework surgery.[2-4] The technique of inducing voice change by the application of pressure to the anterior larynx was first described by Gutzmann[5] in 1910 as a diagnostic test for postmutational falsetto voice. Brodnitz[6,7] in 1958 advocated a similar "pressure test" for differentiating mutational voice disorders from those found in functional dysphonia. Speech pathologists continue to use the technique in the evaluation and treatment of mutational voice disorders.

The laryngeal manual compression tests are simple to perform, require no special instrumentation, and are noninvasive. The tests consist of the following: 1) lateral manual compression, 2) cricothyroid approximation, 3) combined lateral compression and cricothyroid approximation, and 4) anteroposterior compression (Brodnitz test). They are especially useful for patients with incomplete glottic closure, as in symptomatic unilateral vocal cord paralysis, vocal cord atrophy, sulcus vocalis, androphonia in women, and mutational voice disorders in men.

In this study, quantitative changes in phonatory function resulting from lateral manual compression are compared with videostroboscopic, aerodynamic, and acoustic parameters.

LATERAL MANUAL COMPRESSION TEST

The patient is asked to sustain /a/ phonation or maintain running speech during the examination. The examiner's thumb and forefinger are used in the examination. The thyroid ala is identified by landmarks consisting of the superior notch and inferior border. Firm medial pressure is applied to the thyroid lamina at the level of the vocal folds (Fig 1A) in an effort to close the glottic gap caused by lateral displacement and bowing (Fig 1B). Pressure must be sufficient to produce medialization. However, this may not be feasible in older patients, especially men, owing to excessive calcification. In addition, in patients with short thick necks and in young women, the thyroid notch may be difficult to identify. In these circumstances, the examination is repeated in different positions until the best possible results are attained. The effect on the mucosal wave is verified by the use of videostroboscopy. Acoustic and aerodynamic analyses give further confirmation and serve as baseline quantitative measurements for comparison following surgical procedures.

PATIENTS AND METHODS

PATIENTS

Ten patients with hoarseness and incomplete glottic closure were examined. There were eight men and two women, 22 to 70 years of age (see Table).

From the Department of Otolaryngology and Ames Vocal Dynamics Laboratory, Lenox Hill Hospital, New York, New York (Blaugrund, Taira, El-Assuooty, Lin, Gould), and the Department of Plastic Surgery, Kyoto University, Kyoto, Japan (Isshiki).

Presented at the meeting of the American Laryngological Association, San Francisco, California, April 1-2, 1989.

REPRINTS — Stanley M. Blaugrund, MD, Dept of Otolaryngology, Lenox Hill Hospital, 100 E 77th St, New York, NY 10021.

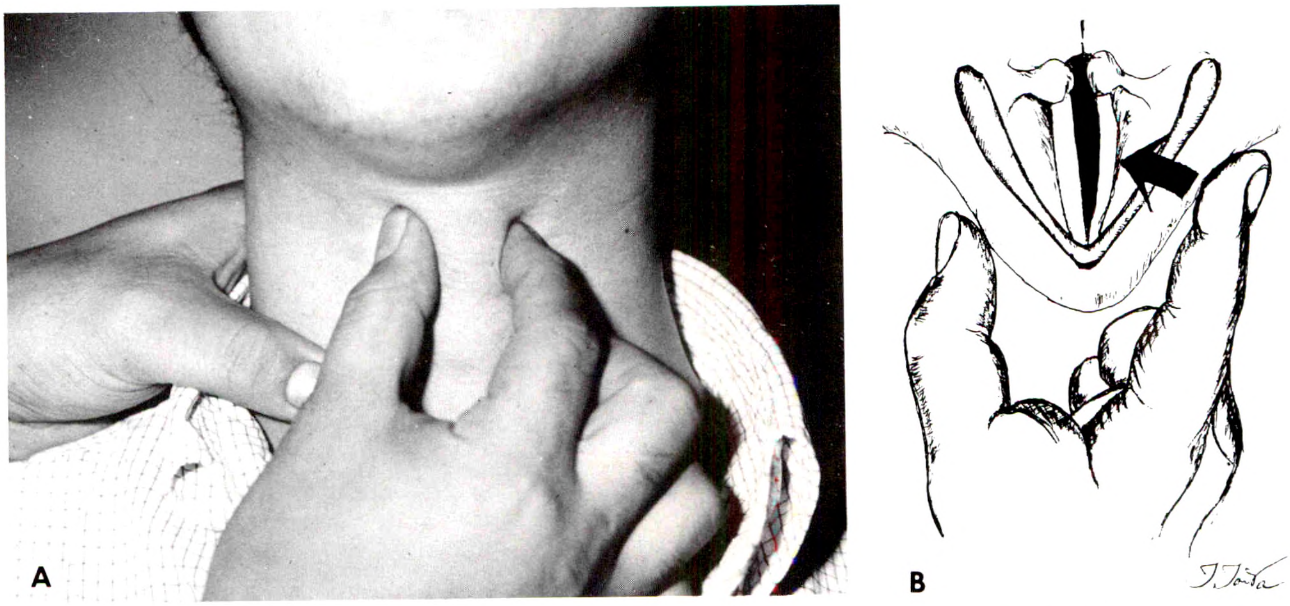

Fig 1. Lateral manual compression test. A) Applied while patient sustains /a/ phonation or maintains running speech. B) Representation of examination as repeated in different positions until glottic gap is closed or best results are attained.

Vocal Fold Atrophy (VFA). Seven patients had VFA of various causes. In this group of patients, one elderly man (patient WW) had presbylaryngis with bowing and atrophy of both vocal folds, and patients TA and TC, who had previously sustained laryngeal trauma requiring tracheostomy, presented with VFA. Two patients, a man and a woman, had previously undergone vocal cord surgery (patient FB, polypectomy, and patient MB, Teflon injection). Patient SM was HIV-positive and had concurrent multiple sclerosis. Patient SS, the final patient in this group, presented with an undiagnosed myopathy.

Recurrent Laryngeal Nerve Paralysis (RLNP). Three patients had RLNP: patient AC had sustained laryngeal trauma in a vehicular accident, patient IS had recently undergone cervical diverticulectomy, and patient SG had RLNP of an undetermined cause and was suffering from Lyme disease.

ANALYSIS OF PHONATORY FUNCTION

Videostroboscopic Analysis. Video documentation of patients before and after lateral manual compression was performed in the following manner. After decongestion of the nasal membrane with phenylephrine hydrochloride (Neo-Synephrine 1%) and application of light topical nasal anesthesia (lidocaine hydrochloride [Xylocaine] 1%), fiberoptic laryngoscopy was carried out with use of the Olympus fiberoptic nasopharyngoscope ENF, type P2. When a satisfactory image was obtained, a video camera (Ikegama, model MK 309C) was applied to the endoscope, which in turn was attached to the stroboscope (Bruel & Kjaer, No. 4914). The analyses continued until documentation was complete.

Aerodynamic Analysis. In the aerodynamic analysis, the mean airflow rate (MFR) was equal to the phonation volume (PV) divided by the maximum phonation time (MPT). The phonation quotient (PQ) was equal to the vital capacity (VC) divided by MPT. The vocal velocity index (VVI) was equal to MFR divided by VC times 1,000.

Maximum phonation time, to some degree, is important as an indication of glottic competency and the ability to conduct normal conversation.[8-11] It is also greatly influenced by VC. Patients were asked to hold /a/ in a natural speaking voice for as long as possible while being timed. Vital capacity was determined with a spirometer, and the percentage of predicted volume was calculated by standard means. Normal range in women is 14 to 40 seconds and in men is 15 to 62 seconds.

Mean airflow rate is a good indicator of the degree of glottic closure. For example, MFR is high in unilateral RLNP because of poor glottic closure and correspondingly low in spastic dysphonia because of glottal hyperfunction. The degree of closure was measured by use of a spirometer. In women, the normal range is 43 to 193 mL/s, and in men, it is 46 to 222 mL/s.

Phonation quotient, another measure of airflow rate, represents a ratio of VC and MPT (PQ = VC/MPT). According to Iwata and von Leden,[12] PQ is a less sensitive indicator of glottic airflow than MFR. In 1970, these authors compared the PQ in patients with various pathologic lesions of the larynx with PQ values obtained in normal subjects and found that the mean value of the PQ was significantly higher than that of the control subjects at the .05 level of significance, except in patients with contact

MANUAL LARYNGEAL COMPRESSION TEST PATIENTS

Patient	*Age (yr)*	*Sex*	*Pathologic Condition*	*Cause of Disorder*	*Surgical Procedure*
TA	31	M	VFA, R	Trauma	
IS	63	M	RLNP, L	Zenker's diverticulum	Thyroplasty
FB	53	F	VFA, bilat	Polypectomy	
SS	45	F	VFA, L	Myopathy	
SM	32	M	VFA, L	Multiple sclerosis, HIV	
WW	70	M	VFA, R	Presbylaryngis	
MB	49	M	VFA, L	Teflon injury	Thyroplasty
SG	47	M	RLNP, L	Lyme disease	
AC	42	M	RLNP, L	Trauma (11 yr)	Thyroplasty
TC	22	M	VFA, bilat	Trauma (12 yr)	Thyroplasty

VFA — vocal fold atrophy, RLNP — recurrent laryngeal nerve paralysis, bilat — bilateral, R — right, L — left.

granuloma, and they found no sex-linked differential in PQ among the group of patients tested.

Vocal velocity index is a ratio of MFR to VC during sustained phonation. Koike and Hirano[13] in 1968, examining 42 normal subjects, determined that there was no statistical difference in their experimental findings between men and women. The actual range of the VVI was 14.1 to 45. Their data suggested no sex differential, and the test was felt to be a sensitive indicator of normal and abnormal vocal function. The VVI is expected to be low in strained voices and higher in breathy, asthenic voices.

Acoustic Analysis. Voice quality during lateral manual compression was recorded in a soundproof booth with a microphone (Electrovoice model 666) and an open-reel tape recorder (Otari Mx 5050). A mouth-to-microphone distance of 20 cm was maintained throughout each session. Comfortable vocal pitch and intensity were established, and the patient was asked to sustain /a/ phonation while lateral manual compression was administered. To obtain further information on voice quality, sound spectrographic analysis was carried out with use of the Kay Elemetrics DSP Sona-Graph, model 5500.

Perceived voice quality analysis was performed by trained observers in the laboratory. Tapes were judged for degrees of roughness and breathiness in each of the subjects recorded. The degrees of roughness and breathiness were rated 0 = normal, 1 = slight, 2 = fair, and 3 = extreme.

Sound spectrographic analysis was carried out according to Yanagihara's[14,15] four-type rating, which is based on the degree of harmonics and of noise components through a wide frequency band (0 Hz to 8 kHz).

The breathiness (Br) and strain (St) indices were described in a study reported by Fukazawa et al[16] in 1988. The Br index reflects the degree of high-frequency noise component in the voice wave. This high-frequency noise component is proportional to the amount of turbulent noise created by a glottic gap. The St index connotes the relative strength of vocal energy in the voice wave and expresses the result of increased tension of the vocal cords in the presence of high subglottic pressure. Analyzed by computer, these tests are sensitive indicators of turbulent noise, vocal cord tension, and irregular vibration; they were introduced in an effort to "identify more objectively, hoarse voice qualities."[16] Breathiness and strain, along with jitter, were used in the analysis of hoarseness in 39 patients. A significant finding in the study was that a relatively high degree of breathiness was associated with carcinoma of the larynx. However, there were also close correlations in patients with vocal cord polyps and RLNP.

RESULTS

Mean Airflow Rate and Maximum Phonation Time. Mean airflow rate was significantly reduced in all patients who underwent lateral manual compression (Fig 2A). Patients IS and TC had persistently high MFRs despite lateral manual compression. Patient IS had paramedian left RLNP following excision of a Zenker's diverticulum, and patient TC had VFA with scar resulting from laryngeal trauma 12 years before. As might be expected, MPT increased as MFR decreased (Fig 2B). In three patients, MPT failed to return to normal despite lateral manual compression. These three were patients IS, TC, and SS, a woman with an undiagnosed fluctuating myopathic disorder, whose vocal analysis varied considerably from time to time.

Phonation Quotient and Vocal Velocity Index Analysis. Figure 2C shows PQ with and without lateral manual compression. Clinically, values exceeding 300 mL/s are considered abnormal. The PQ, since it is highly influenced by MPT, would be expected to show high values in patients with large glottic gaps. And again, patients IS and TC are outside the normal reference range. This confirms, as did MFR and MPT, the presence of significant glottic gaps in these two patients. The VVI (Fig 2D) as reported by Koike and Hirano,[13] is a more sensitive indicator of aerodynamic function than is the PQ. This appears to be so, since half the patients tested exceeded the normal value of 14.1 to 45.

Sound Spectrograms. With lateral manual com-

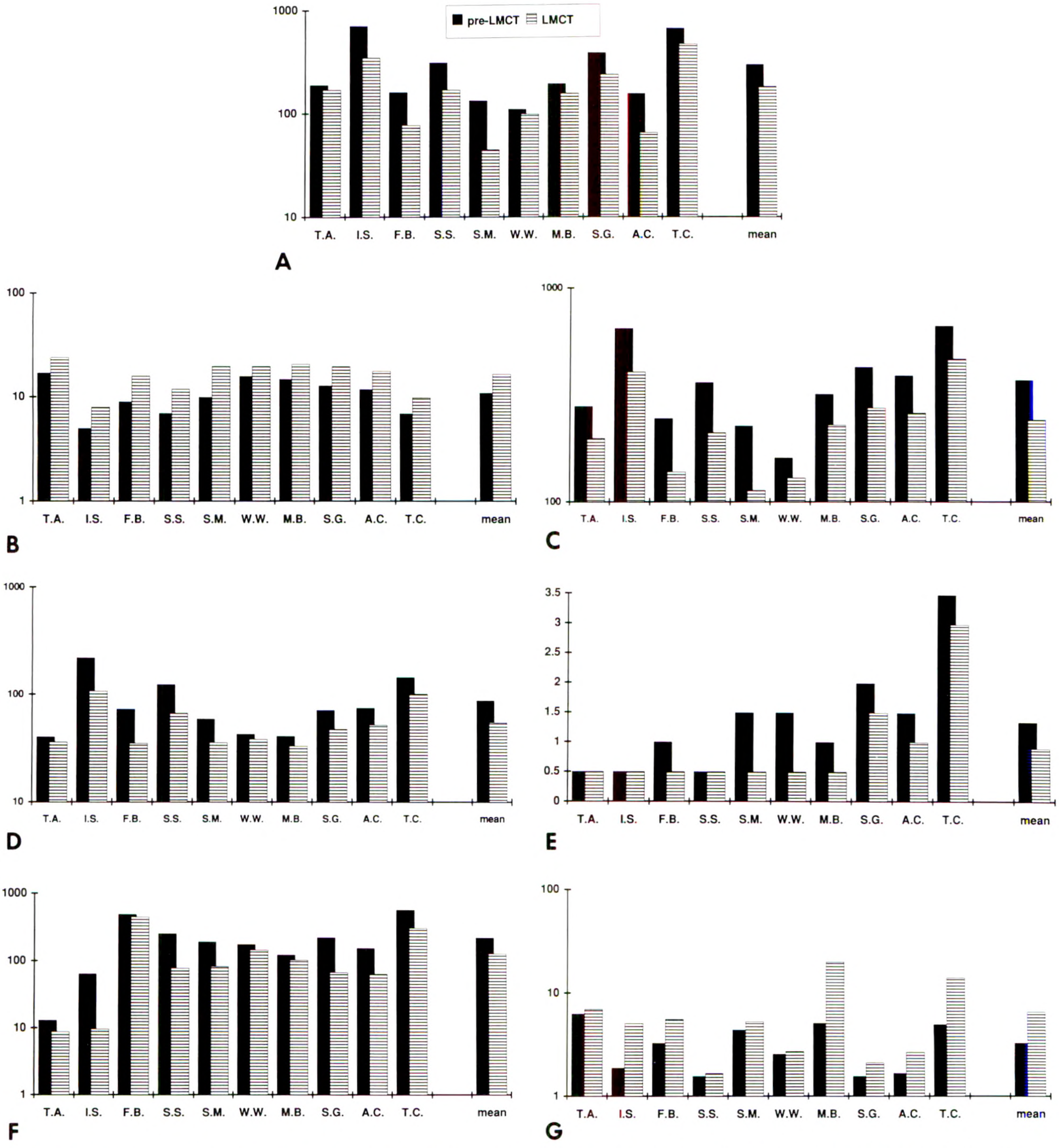

Fig 2. Computer graphics. A) Mean airflow rate. Reduction in all patients during lateral manual compression tests (LMCTs) is shown. Patients IS and TC showed persistently high airflow rates. Both had large glottic gaps. Patient TC had stiffness from scar from previous laryngeal fracture. B) Maximum phonation time (MPT). Expected increase in MPT as result of LMCT is shown. Patients IS and TC again failed to respond. C) Phonation quotient (PQ). Influence by MPT reveals expected high airflow in patients with large glottic gaps. Values above 300 mL/s are considered abnormal. D) Vocal velocity index (VVI). It is more sensitive indicator of glottic airflow than is PQ. Over half of patients exceeded high normal level of 45 in pre-LMCT status. LMCT produced good responses except in patients IS and TC. E) Sound spectrography findings. Three patients had no recovery; all three had recurrent laryngeal nerve paralysis. F) Breathiness index. Index was high in almost all patients before LMCT. Closure of glottic gaps by LMCT produced good response in most patients. G) Strain index. Index is low in comparison to breathiness index. Patient MB, who had had previous Teflon injection, shows dramatic increase in strain index with LMCT.

pression, seven patients were classified as type 0.5 on a scale of 0 to 4. The sound spectrograms confirmed that glottal gaps accounted for most of the noise components in the voices of the patients tested (Fig 2E). Three patients (SG, AC, TC) evidenced no recovery in their sound spectrograms with lateral manual compression. Two of these patients had sustained previous laryngeal trauma and the third was suffering from Lyme disease. We feel that there may be four possible reasons for this lack of im-

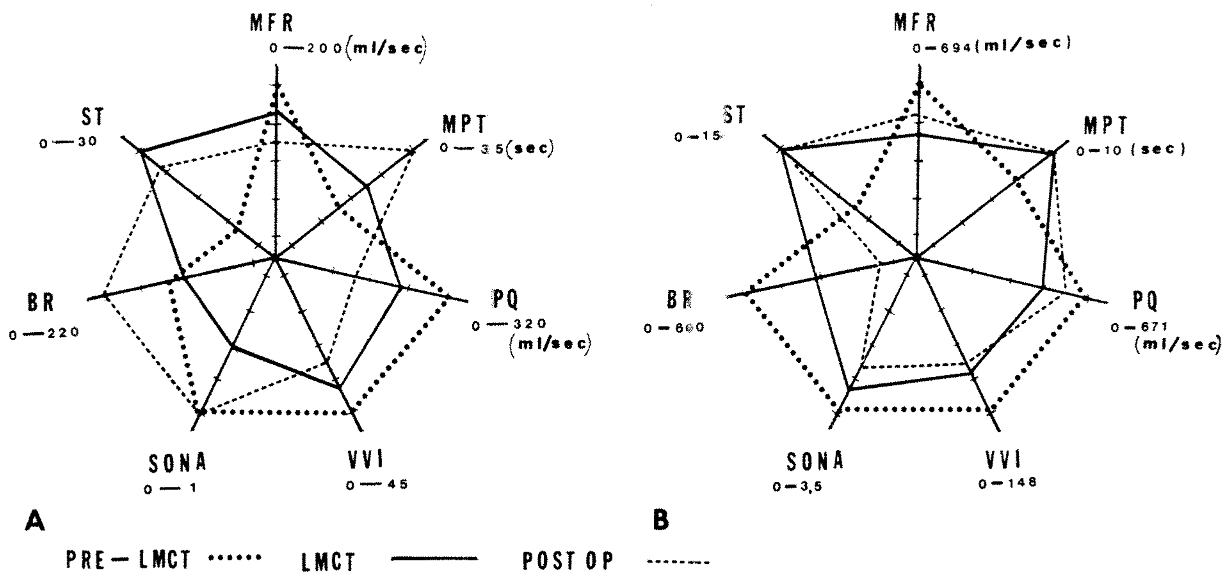

Fig 3. Radial axis graphs 1 month following Isshiki thyroplasty type I. A) Patient MB. Voice is improved subjectively and objectively despite presence of bolus of Teflon beneath left vocal fold. B) Patient TC. Thyroplasty revision was required and deeper prosthesis was inserted.

provement: 1) ineffectively applied pressure, 2) wrong position on the thyroid ala, 3) excessive calcification of the thyroid cartilage, and 4) splinting of the strap muscles, limiting the effectiveness of the pressure. There may be other factors that have not been identified.

Breathiness and Strain Indices. Figure 2F,G reveals the relationship between the Br index and the St index with and without lateral manual compression. In RLNP the Br index is high, while the St index is low. In VFA, the Br index is relatively higher than in RLNP. The St index, however, remains essentially unchanged from that seen in RLNP. With the application of lateral manual compression, the Br index decreased, while the St index increased. In some patients the St index increases to such an extent that voice quality becomes distorted. In this instance, LMCT is less reliable in predicting the outcome of surgical procedures. We have observed this phenomenon in patients who have previously undergone thyroplasty type I; strain, which initially increased, gradually decreased over a period of months as patients became more accustomed to their voices. Presumably, in time they were better able to modulate their voices, owing to improved vocal efficiency. Breathiness, on the other hand, decreased after surgical procedures and has remained decreased in these operated patients.

Results of Thyroplasty. Since the inception of this investigation, 4 of the 10 patients evaluated have undergone Isshiki thyroplasty type I: patients MB, IS, AC, and TC. All 4 were felt to be acceptable candidates for medialization on the basis of the results of lateral manual compression. We have excluded patients AC and IS for the following reasons: patient AC lives in another state and has not been able to return for testing, and IS underwent a surgical procedure on March 7, 1989. It is too early to perform postoperative tests, but subjectively he has had a satisfactory initial response. The postoperative results of both these patients will be added in subsequent reports of this ongoing study.

Patient MB underwent Isshiki thyroplasty type I on Nov 15, 1988. The postoperative result at this time is considered satisfactory as evidenced by improved objective test results following the procedure (Fig 3A). If one takes into account the fact that this patient's left vocal cord had previously been injected with Teflon, the normalization of his aerodynamic and acoustic parameters only 1 month after the operation is encouraging. Voice quality, however, remains slightly impaired, as evidenced by a residual value of 1.5 on the sound spectrogram scale of 0 to 4, 0 being normal. This patient was considering resignation from a position of high responsibility because of his perception that he was communicating ineffectively. As a result of medialization surgery, his voice has improved, he is more effective in his occupation, and his perception of his ability to communicate has changed.

Patient TC underwent Isshiki thyroplasty type I on Dec 6, 1988. There was excellent improvement in voice on the operating table and immediately postoperatively (Fig 3B). However, in subsequent weeks after the operation, it was evident that although the patient's voice was improved, some breathiness persisted, and on Feb 21, 1989, the patient underwent revision thyroplasty type I. The original prosthesis was removed and another, twice as deep, was inserted, with immediate improvement in voice quality. After the larger prosthesis was in position, cricothyroid approximation was attempted (thyroplasty type IV) and even greater improvement was noted. The patient remains under observation. His voice is excellent.

In evaluating this patient retrospectively, it is notable that he was one of two patients whose MFR remained high despite lateral manual compression. This leads us to postulate that the glottic gap was too large to close effectively by lateral manual compression. Under the circumstances, perhaps this finding warrants the performance of bilateral medialization or arytenoid adduction at the outset, since the adduction procedure brings the vocal cord to the midline more effectively than does thyroplasty type I.

DISCUSSION

Suspended within the larynx as though they were elastic bands, the vocal folds are easily influenced by indirect modifications of the laryngeal framework. Data obtained in this investigation reveal that lateral manual compression produced significant changes in aerodynamic factors and in acoustic characteristics of the voice signal. It is the change in shape, tension, and position of the folds brought about by these alterations that forms the basis for medialization laryngoplasty. Lateral manual compression is a means of obtaining preoperative information that might be useful in predicting the outcome of a surgical procedure.

In all of the 10 patients evaluated in this study, hoarseness was ascribed to imperfect glottic closure, with or without stiffness brought about by spontaneous atrophic changes or by previous trauma or a surgical procedure. In one patient (MB), hoarseness was attributed to both incomplete glottic closure and stiffness resulting from the previous Teflon injection.

Favorable alterations in the aerodynamic parameters tested in these patients achieved by lateral manual compression suggested that surgical medialization procedures would be beneficial in the restoration of phonatory efficiency. During lateral manual compression, most patients were capable of producing a more forceful, resounding voice with less obvious effort. Among the 10 patients tested, there were 2 in whom there was failure to obtain satisfactory reduction in glottic airflow during lateral manual compression. These patients, IS and TC, were believed to have glottic gaps that could not be effectively closed by lateral manual compression. One of these patients, TC, who had bilateral VFA as a result of trauma 12 years before that required tracheostomy, has undergone two attempts at thyroplasty type I. The first procedure failed to close the gap adequately. A larger prosthesis was implanted during the second procedure, apparently with good effect; however, it is too early to evaluate the result. Arytenoid adduction or bilateral medialization might be necessary to fully restore the voice in this patient. We must also consider the possibility that adequate restoration of voice in this patient is not feasible owing to scar and atrophy, the result of the laryngeal fracture that required tracheostomy.

In the case of patient IS (Zenker's diverticulectomy and RLNP), who underwent medialization laryngoplasty on March 7, 1989, we anticipated on the basis of lateral manual compression that he would require a large prosthesis for medialization, and this proved to be the case.

Acoustic parameters are also felt to be useful in assessing patients preoperatively. Breathiness, for instance, is indicative of turbulent air flowing through a large glottic gap. Reduction of the gap with lateral manual compression is a means of decreasing the high-frequency noise component in the voice wave. This high-frequency component (friction noise) is largely responsible for the auditory impression of breathiness. Stronger harmonics with a lesser noise spectrum revealed a higher efficiency of airflow through the vocal tract. Patients who show a significant decrease in the Br index are good candidates for medialization laryngoplasty.

The St index is indicative of high-strength vocal energy in relation to the original voice wave. It is also a good indication of tension in the vocal folds in the presence of high subglottic pressure. In this study, strain increased in all patients. We feel that this is due to the production of stronger harmonics and a high-intensity voice wave. The increase in the St index is due to more effective glottic closure by lateral manual compression. It is worthy of note that patient MB showed the highest increase in St index, probably owing to stiffness as the result of the previous Teflon injection.

Of all the parameters that we have used in evaluating these patients, MFR and MPT appear to be the most reliable.

SUMMARY

Medialization laryngoplasty has aroused interest as an alternative to intracordal injection of Teflon in the management of patients with unilateral RLNP, VFA, and sulcus vocalis. Lateral manual compression as described in this report is an easily performed office procedure that is noninvasive and requires no special instrumentation. For quantification of results, it is recommended that videostroboscopy and basic aerodynamic and phonatory function tests be administered in tandem with lateral manual compression.

Preliminary findings in 4 of 10 patients in this group indicate that when test results are conclusive of effective glottic closure, thyroplasty type I is the procedure of choice. If closure remains incomplete, thyroplasty types I and IV in combination, or arytenoid adduction, should be considered as an alternative method of achieving voice restoration. This study will be augmented by the accumulation of data on additional patients. Data obtained after medialization surgical procedures will be compared with preoperative findings as a means of judging the efficacy of lateral manual compression as a valid method of predicting the outcome of surgical procedures in patients with imperfect glottic closure.

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REQUEST FOR PROPOSALS
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The American Laryngological Association has established a grant for research on laryngology, rhinology, and related subjects. The maximum grant for one year is $15,000. Deadline for submission is June 1, 1990. For the specifics of eligibility and application materials, write to the American Laryngological Association, H. Bryan Neel III, MD, Secretary, 200 First Street, SW, Rochester, MN 55905.

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STAGING FOR CHOLESTEATOMA IN THE CHILD, ADOLESCENT, AND ADULT

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A closed tympanomastoidectomy with subsequent staged surgical procedures leading to the excision of cholesteatoma was validated as described. All elements of staging with a 10-year experience of 354 patients are covered according to categories of child (0 to 9 years), adolescent (10 to 15 years), and adult. The child differed from the adolescent and adult in the following manner: more recurring cholesteatomas, greater ossicular necrosis, poorer hearing results, less aggressive residual cholesteatoma, and significantly poorer results with pars flaccida cholesteatoma than pars tensa cholesteatoma. After the end stage, 90% of the cases remained closed, with acceptable hearing in 60% of the patients.

KEY WORDS — cholesteatoma, recurrent cholesteatoma, recurring cholesteatoma, residual cholesteatoma, staging, tympanomastoidectomy.

The surgical treatment of cholesteatoma has been controversial from the onset. When experienced otologists reach diametrically opposed positions regarding the surgical technique of excising cholesteatoma, the picture is confusing. Could advocates of both open and closed mastoidectomy be right? Should certain cases be opened, others closed?

This study was designed to test the intact canal wall (closed) mastoidectomy, note its failures and successes, and attempt to solve the controversy.

The validation of the excision of cholesteatoma by the closed tympanomastoidectomy rests on two factors. The first is the visual extirpation of the cholesteatoma, noted by the surgeon. The second is the passage of time prior to ascertaining the absence of cholesteatoma. Therefore, two or more staged surgical procedures are necessary to validate the excision of cholesteatoma.[1]

STUDY

This 10-year study (1978 to 1988) follows 354 patients who underwent closed tympanomastoidectomy with subsequent staged surgical procedures 1 year apart until the eradication of cholesteatoma could be validated. These consecutive patients were included in the study because cholesteatoma was present in the middle ear clefts and, usually, the mastoid cavities. The alternative surgical procedure would have been a radical mastoidectomy, following strict surgical practice. Prior to selection, no patient was eliminated because of the amount of cholesteatoma. The criteria for study were the presence of the majority of the posterior bony canal wall and a stapes, or portion thereof, that could transmit sound.

The surgical findings and results are reported in three age categories: children, 0 to 9 years of age (n = 38); adolescents, 10 to 15 years of age (n = 50); and adults, 16 years or older (n = 266).

Although this study spans 10 years, patients entered this study during each of the 10 years. The average follow-up time for all patients was 7 years because of the greater number of cases at the beginning of the 10-year span. There is no significant difference in follow-up time among the age categories.

SURGICAL PROCEDURE

Following common surgical principles, the surgical technique for the primary tympanomastoidectomy consisted of a transcanal tympano-ossiculoplasty with a concurrent isolated postauricular mastoidectomy. The facial recess was approached transmastoid when necessary to remove cholesteatoma. Reconstruction for hearing was performed at the time of the primary operation and adjusted or revised as needed at subsequent procedures. The subtechniques of operation were as follows.

TRANSCANAL

1. Tympanomeatal flap developed to the extent of the perforation.
2. Middle ear and eustachian tube explored and assessed for the extent of the cholesteatoma.
3. Ossicles assessed for necrosis and type of reconstruction.
4. Facial nerve bony canal wall identified and assessed for dehiscence.
5. Cholesteatoma removed from the middle ear cleft.
6. Perforation and middle ear prepared for medial fascia graft.
7. Tragal cartilage removed for canalplasty, if necessary.

From the Warren Otologic Group, Warren, Ohio.

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POSTAURICULAR

8. Layered incisions made for mastoidectomy.
9. Temporalis fascia graft removed for medial grafting transcanal.
10. Mastoidectomy performed to the extent of the cholesteatoma and other disease.
11. Semicircular canals assessed for fistula.
12. Incus removed if necessary.
13. Malleus head removed (nipped transcanal) if necessary.
14. Facial recess opened and explored.
15. Cholesteatoma removed from mastoid cavity.
16. Mastoid incision closed in layers.

TRANSCANAL

18. Perforation grafted medially with a wet fascia graft.
19. Ossicular assembly reconstructed with semibiologic ossicle cup and columella prosthesis.
20. Tympanomeatal flap and graft repositioned.
21. Ear canal packed with Gelfoam and dressing applied.

STAGING PROCESS

The best time to inform the patient of the need for more than one surgical procedure is before any operation is performed. The results and risks of the proposed operation will be discussed in obtaining an informed consent. Therefore, the necessity of multiple surgical procedures is easily addressed. The printed material the surgeon may use for patient education could also include a discussion of staging.

In spite of the surgeon's best educational efforts for follow-up, certain patients will not return for further treatment during the time span for staging. The reasons vary, but circumstances include financial problems, life events, distance, and misunderstanding. A vigorous follow-up campaign should be used and was necessary in 20% of the patients. At the end, including time delays, 92.4% of the patients followed through with the necessary staging. The lost-to-follow-up rate of 7.6% includes two categories of patients: patients at an end stage (5.9%) and those still at risk concerning recurring cholesteatomas (1.7%). About one half of these patients will not experience a problem with cholesteatoma, as this study will reveal.

Surgical experience with patients who underwent a delayed staged surgical procedure, plus the findings of revisions of cases by other surgeons, reveal the same type of complications from recurring cholesteatomas as from acquired cholesteatoma. If recurring cholesteatomas are not treated, central nervous system complications will develop. Perhaps the rate of complications of recurring cholesteatomas is less than that of acquired cholesteatomas, since recurring cholesteatomas can present laterally through the surgical approaches, thus lessening medial extension and damage. But the surgeon must remember that recurring cholesteatomas are not benign in nature.

SURGICAL FINDINGS

PRIMARY ACQUIRED CHOLESTEATOMAS

The site of the primary acquired cholesteatoma is important in reporting the surgical findings of recurring cholesteatomas. Acquired cholesteatoma arises either in the pars flaccida or the pars tensa. Recurring cholesteatomas after removal of a pars flaccida cholesteatoma tend to be, more often than not, recurrent cholesteatoma. Likewise, recurring cholesteatomas after the removal of a pars tensa cholesteatoma tend to be residual cholesteatomas. Therefore, the incidence of the originating cholesteatoma is important in age group comparisons.

The incidence of a pars flaccida cholesteatoma in this study was as follows: child, 31%; teen, 38%; adult, 44%. The incidence of pars tensa cholesteatoma was as follows: child, 69%; teen, 62%; adult, 56%. The obvious trend is that the older the patient, the greater the incidence of pars flaccida cholesteatoma. Whether this finding is a function of a greater length of time of eustachian tube dysfunction is unclear. The point for a surgeon is that fewer pars flaccida cholesteatomas will be found in children than in adults; and the incidence of recurrent cholesteatomas, and perhaps retraction pockets, could be less in children than in adults. The opposite hypothesis concerning pars tensa cholesteatoma and residual cholesteatomas is also valid.

The following data concerning surgical findings do not yield valid statistics because of the uneven number of patients in the three age groups.

RECURRING CHOLESTEATOMAS

Five categories of surgical findings were noted at the time of the staged surgical procedure. The decisions for patient care are discussed for each category.

Negative Finding. The goal of the surgeon is to achieve an ear that is well healed with no visual evidence of recurring cholesteatomas. When this situation is encountered, the surgical finding is labeled "negative findings." The excision of the cholesteatoma was validated, and no further surgical procedure was necessary.

Squamous Pearl. An encapsulated form of residual cholesteatoma is called "squamous pearl." A squamous pearl is a small, white, round object that resembles a pearl. The squamous pearl probably represents a self-contained form of residual cholesteatoma that is stable. The pearl and its base are removed, and no further surgical procedure is planned. Thus, the patient with a finding of one or more squamous pearls is at an end stage.

TABLE 1. PERCENTAGE OF PATIENTS WITH RESIDUAL CHOLESTEATOMA AT SECOND-STAGE OPERATION

Age Group	*Pearls*	*Residual*	*Total*
Child	40	9	49
Teen	13	27	40
Adult	20	12	32

TABLE 2. PERCENTAGE OF PATIENTS WITH RECURRENT CHOLESTEATOMA AT SECOND-STAGE OPERATION

Age Group	*Retraction*	*Recurrent*	*Total*
Child	3	21	24
Teen	7	20	27
Adult	14	12	26

Residual Cholesteatoma. When cholesteatoma is found in any form other than a pearl, and hidden under an intact tympanic membrane, it is called "residual cholesteatoma." The cholesteatoma is removed, and a third-stage surgical procedure is planned in order to validate the complete excision of the cholesteatoma.

Retraction Pocket. The finding of a retracted tympanic membrane forming a dry pocket could be an early recurrent cholesteatoma, yet some retraction pockets appear stable in size. A retraction pocket, by definition, is empty and easily removed, usually intact. When found, it is removed and excised, the tympanic membrane regrafted, and the area bridged by a tragal cartilage graft. Since a retraction pocket is easily recognized and followed up in the office, no further surgical procedures are planned. The patient with a retraction pocket is also at an end stage.

Recurrent Cholesteatoma. A recurrent cholesteatoma has the same appearance as an acquired pars flaccida cholesteatoma. The use, at the initial surgical procedure, of a tragal cartilage graft blocking the pars flaccida has greatly reduced the incidence of this finding. The surgeon must make the decision either to convert the tympanomastoidectomy from a closed to an open one, or continue staging.

In sum, the surgical findings after a closed tympanomastoidectomy include one category of negative findings and four categories of positive findings: squamous pearl, residual cholesteatoma, retraction pocket, and recurrent cholesteatoma. The patient is at end stage with the surgical findings of three categories: negative findings, squamous pearl, and retraction pocket.

SECOND-STAGE SURGICAL FINDINGS

Negative Findings. Of the 298 patients who underwent a second-stage procedure, an average of 37% had an intact tympanic membrane with no visual evidence of cholesteatoma. In comparing age groups, children had a lesser rate of negative findings of 27%, teens a little more with 33%, and adults the greatest rate of 42%. The conclusion is that the child and teen have a greater tendency for recurring cholesteatomas.

Squamous Pearl. The incidence of a squamous pearl was 21% overall for the study (Table 1). However, the greater rate for this surgical finding was in children, with 40%; adults had only 20%. That children had twice the rate of squamous pearls may mean that residual cholesteatoma is less aggressive in the child than in the older population. The overall incidence of residual cholesteatoma is best compared with the next category.

Residual Cholesteatoma. When a large amount of hidden cholesteatoma is found, the patients fall into this category (Table 1). The greatest incidence was teens at 27%, with adults lower at 12%, and the children at 9%. Adding both categories of squamous pearl and residual cholesteatoma, there are differences among the three age categories. The incidence of residual cholesteatoma, including squamous pearl, is greater for the child and teen, but appears less aggressive in the child.

Retraction Pocket. The surgical finding of a pocket in the tympanic membrane is lowest in the child at 3%, and increased in teens at 7% and the adult at 14% (Table 2). Adding this category to the recurrent cholesteatoma category may yield some understanding of retraction pockets.

Recurrent Cholesteatoma. Children appear to have more recurrent cholesteatoma than adults, 21% as compared to 12%, but if we add the category of retraction pockets to recurrent cholesteatoma, there is no difference among the age groups (Table 2). However, the incidence of pars flaccida cholesteatoma is less for the child. Therefore, the child has a greater chance for recurrent cholesteatoma.

The patients with a cholesteatoma arising from the pars flaccida were compared to those with cholesteatomas arising from the pars tensa in all age categories. The only significant finding was in children. Not only is the incidence of pars flaccida cholesteatoma greater in a child, but the surgical results are worse. A child is twice as likely to need a third-stage surgical procedure as the child with a pars tensa cholesteatoma. Also, a child with a pars flaccida cholesteatoma is twice as likely to need to be converted to an open mastoidectomy.

In the end, only 50% of the children with recurrent pars flaccida cholesteatomas maintained a closed tympanomastoidectomy. A likely conclusion may be that the closed mastoidectomy is not feasible for a pars flaccida cholesteatoma in a young child. But, with this knowledge, can the technique be changed to ensure greater success?

While all patients underwent a second-stage surgical procedure, only 14% of the adults needed a third-stage procedure. The child and teen had a

35% rate for a third step, adding validity to the statement that children have more recurring cholesteatomas than adults.

The overall conversion (closed to open) rate also was 6% after the second stage. The incidence was greater in the child, at 15%.

THIRD- AND FOURTH-STAGE SURGICAL FINDINGS

Curiously, the incidence of negative findings at the third stage was the same as that at the second stage, except for teens, who increased the rate from 33% to 57%. The significance of this finding is unknown. But the same incidence does indicate that the surgeon has limitations on his ability to ensure the complete excision of cholesteatoma with one surgical procedure. The number of patients that underwent a third stage was 55, thus providing no significant data in the four positive-finding categories.

To date, only several patients have undergone a fourth-stage surgical procedure in the quest to validate the excision of cholesteatoma. The surgical findings were benign, and therefore, fourth stages are no longer a planned event.

HEARING RESULTS

The hearing results were derived by comparing the preoperative and postoperative hearing levels of the pure-tone averages of three speech frequencies (500, 1,000, and 2,000 Hz). Postoperative hearing results compare the postoperative air hearing level with the preoperative bone hearing level and are reported as modifying the air-bone gap by the following categories:

1. Within 10 dB: postoperative air hearing level within 10 dB of preoperative bone hearing level.
2. Within 20 dB: postoperative air hearing level within 20 dB of preoperative bone hearing level.
3. Within 30 dB: postoperative air hearing level within 30 dB of preoperative bone hearing level.
4. Over 30 dB: none of the above categories.

All of the testing was done in a standard audiometric setting with a common audiometric testing technique. If discrimination scores showed a loss greater than 15%, the patient's hearing results were considered unsuccessful.

The category of "within 20 dB" encompasses the outcomes accepted as successful hearing results. Although the category of "within 30 dB" is also reported as partial success, these patients usually undergo a revision surgical procedure to obtain better hearing. The opportunity to obtain better hearing by revision of the ossicular assembly naturally exists at each staged surgical procedure. However, only a 5% average gain in hearing was realized with revision.

The success of the hearing results after a closed tympanomastoidectomy depends both on effective closure of the perforated tympanic membrane and on the specific technique of ossicular reconstruction. First, the closure rate of the perforated tympanic membranes was 89%. The perforation rate was twice as high in the child as in teens or adults. The 11% of patients with postoperative perforations underwent a revision tympanoplasty at a subsequent staged surgical procedure. These patients were not singled out and are included in the overall hearing results. Second, three categories of ossicular problems were encountered and reconstructed: absent stapes superstructure (2%), absent long process of the incus (58%), and a combination of both (32%). No ossicular disease was found in 7% of the patients. When a stapes superstructure was absent, a modified Robinson stapes prosthesis was placed on the footplate and attached to the incus.[2] The majority of the patients needed an incus replacement prosthesis, and a semibiologic prosthesis, the ossicle cup, was used in the reconstruction. Likewise, the ossicle columella prosthesis was used to replace the stapes superstructure and absent incus. A semibiologic prosthesis incorporates a synthetic portion (Teflon) into the remaining ossicle (incus body or malleus head) or into an ossicle homograft.[3] This assembly is then positioned as one unit.

In a comparison of the age groups according to the type of prosthesis used and thus the amount of ossicular necrosis, a significant trend was noticed. The children had a greater number of total ossicular replacement prostheses used in reconstruction. Since the cholesteatoma is present for less time than in the older groups and the ossicular damage is greater, we conclude that cholesteatoma in the child may be more aggressive.

All prostheses have an extrusion rate, and the time span of this study covers the window of opportunity for extrusion. The extrusion rate was 2%, the same rate as experienced with the homograft ossicle alone. Extrusions are more frequent with the ossicle columella than the ossicle cup prostheses.

After the first stage, 58% of all the patients were within 20 dB of the preoperative bone level. Children had the least hearing gain of 45%, and teens the best hearing at 66%. Comparing hearing within 10 dB, the child also had the worst incidence of 16%. Yet, within 30 dB, there was no difference among the age groups.

After the second stage, the hearing was better, as adjustments to the ossicular assembly could be made (Table 3). Within 20 dB, children were at 57%, teens at 80%, and adults at 59%. Overall, the rate of closure within 20 dB was 63%, a 5% gain over the first-stage results of 58%. There is not a significant difference among age groups after the second stage.

TABLE 3. HEARING RESULTS AT SECOND-STAGE OPERATION

*Category**	*Child* (%)	*Teen* (%)	*Adult* (%)	*All Ages* (%)
Within 10 dB	30	58	37	40
Within 20 dB	57	80	59	63
Within 30 dB	72	89	77	80
Over 30 dB	28	11	23	20

*See text for definitions.

CONCLUSIONS

This study has shown that recurring cholesteatomas differ depending on the origin of the cholesteatoma. Cholesteatomas arising in the pars flaccida lead to recurrent cholesteatoma, while cholesteatomas arising in the pars tensa lead to residual cholesteatoma. Another fair conclusion is that residual cholesteatoma is found more often in the middle ear cleft than the mastoid cavity. Conversely, recurrent cholesteatoma is primarily found in the mastoid cavities.

Most important, cholesteatomas of any type cause the same complications. Although circumstances differ for each case, severe complications can be seen from recurring cholesteatomas.

A common belief is that children do not differ from adults concerning the surgical treatment of cholesteatoma. In this study, the young child does differ from the teen or adult, although a closed tympanomastoidectomy is not contraindicated. The young child has a lesser incidence of pars flaccida cholesteatoma, but this type of cholesteatoma is more persistent when present and leads to more conversion to "open" cases. Primary acquired cholesteatomas appear more aggressive in the child, as seen by greater ossicular necrosis, which results in less successful hearing results. Overall, the child has more recurring cholesteatomas and problems. Eustachian tube dysfunction may be the cause for a greater perforation rate, as well as for the persistence of recurrent cholesteatoma.

Finally, the question pertaining to the controversy surrounding cholesteatoma remains: is the closed tympanomastoidectomy a natural evolutionary step in the surgical treatment of cholesteatoma, or is it an aberration? The authors are still committed to the closed tympanomastoidectomy, since 90% of the cases remain closed with normal function, and 63% of the patients had acceptable hearing within 20 dB.

Can we do better in the future? Legitimate questions do remain and have to be resolved in order for the closed tympanomastoidectomy to be accepted by all surgeons. Could it be that we will use the closed tympanomastoidectomy with staging for cholesteatomas that arise in the pars tensa, and the open tympanomastoidectomy for cholesteatomas that arise in the pars flaccida? Certainly, the age of the patient and the origin of the cholesteatoma must be considered when choosing a surgical technique for the excision of cholesteatoma.

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CLINICAL DIAGNOSIS OF ANTERIOR INFERIOR CEREBELLAR ARTERY THROMBOSIS

AUTOPSY AND TEMPORAL BONE HISTOPATHOLOGIC STUDY

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A patient having the diagnosis of an anterior inferior cerebellar artery insufficiency died 36 hours after the onset of the symptoms that allowed this diagnosis. The special features of this study include a known symmetric 40-dB hearing loss 1 year prior to the onset of the symptoms, the noted decrease in hearing and severe vertigo heralding the vascular accident, the ensuing neurologic deficits, and the short duration of the patient's life after the onset of her symptoms. The patient's clinical course and the histopathologic findings of the brain stem involved the vestibular nuclei, facial nerve, nuclei of nerve V, restiform body and middle cerebellar peduncle and labyrinth including loss of sensory epithelium of the cochlea and vestibular system and the ganglion cells of Scarpa's ganglion. These findings are correlated with previous animal studies and those of Reye's syndrome. To the authors' knowledge this is the first report of a temporal bone histopathologic study from a patient having had the diagnosis of a labyrinthine arterial vascular accident.

KEY WORDS — anterior inferior cerebellar artery insufficiency, hearing loss, temporal bone histopathology, thrombosis, vertigo.

In 1936 Goodhart and Davison[1] described a single case of thrombosis of the anterior inferior cerebellar artery (AICA) and the signs and symptoms necessary for its diagnosis. The diagnosis of their case was suggested by autopsy findings of the nervous system. A report by Adams[2] further clarified details covering this disorder.

Although hearing loss and vertigo are key elements of criteria necessary for the diagnosis of AICA thrombosis, no temporal bone histopathologic study has been reported for this entity. It is the purpose of this paper to report the temporal bone and CNS autopsy findings from a patient who died 36 hours after the onset of a vascular event diagnosed as thrombosis of the AICA. The labyrinthine findings will be compared to those produced experimentally in guinea pigs by occlusion of the AICA,[3,4] and the findings in human temporal bone studies of Reye's syndrome.[5]

CASE REPORT

This 69-year-old woman was admitted to Albert Merrit Billings Hospital of the University of Chicago for treatment of congestive heart failure by modification of fluid and salt intake, and treatment of signs of digitalis toxicity. She was known to have steroid-induced diabetes mellitus and a nonfunctional thyroid nodule. There was evidence of an old anterior septal myocardial infarct and occasional premature ventricular contractions. A pleural effusion was demonstrated on a chest radiograph. She had normal results on a sensory and motor neurologic evaluation. One year before admission an audiogram had demonstrated a symmetric sensory hearing loss of 40 dB (Fig 1).

By the fourth day of hospitalization her congestive heart condition had improved symptomatically. On the fifth day her pulse was irregular and rapid; however, she had no dizziness or shortness of breath. She could walk to the bathroom with less exertion than was required 5 days earlier.

By the sixth day of hospitalization she was ambulating in her room. At midnight of the sixth day she was found by the nurse to be "sitting in bed with difficulty balancing." She was unable to respond verbally but could grasp hands on command. She started to thrash about and was incontinent of urine. She could move all extremities. Physical ex-

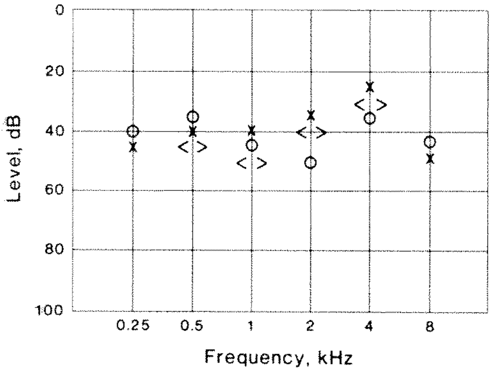

Fig 1. Audiogram showing sensory hearing loss of 40 dB 1 year before admission.

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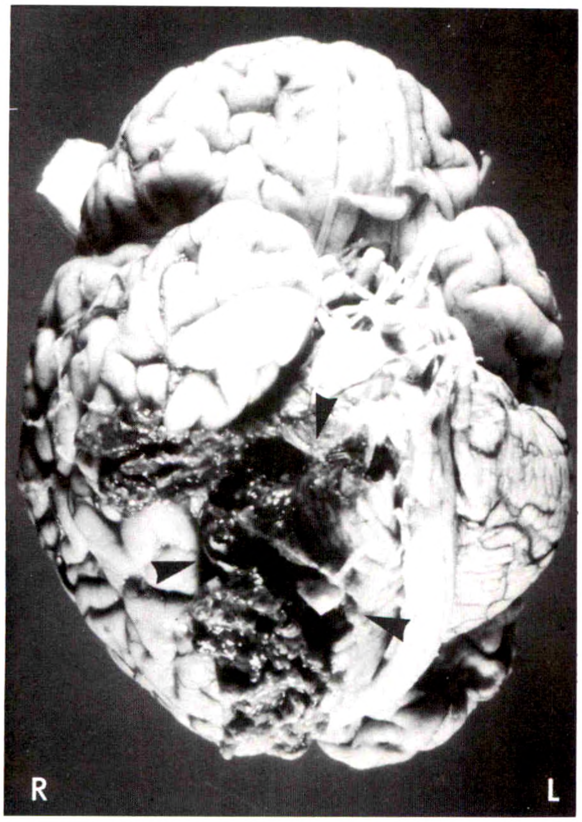

Fig 2. Photograph of basal surface of brain, showing large hemorrhage (arrowheads) involving right side of cerebellum and pons. R — right side, L — left side.

amination revealed a right-sided facial paralysis, decreased motor function of the right side of her body, deviation of the tongue to the right, and atrial fibrillation.

At midday on the seventh day a neurologic evaluation revealed an ability to respond to single commands. There was a right sixth nerve palsy, decreased sensation of the right side of the face (sensory portion of fifth nerve), a normal corneal reflex, an upward rotatory nystagmus, a right lower motor neuron deficit of the seventh nerve, and decreased hearing on the right.

Two hours later there was a right and left sensory deficit of the fifth nerve, indicating further involvement of the pons.

Late that afternoon a lumbar puncture was performed that produced clear spinal fluid having 100 mg% protein. She received heparin for the apparent progressive thrombosis.

Three hours after the onset of heparin therapy the patient had blood in her urine. She again had an episode of "thrashing about" — an apparent second neurologic event.

Eight hours later, now 29 hours after the initial neurologic event, she developed a severe aspiration pneumonia. At 31 hours she had a deteriorating neurologic status with unequal pupils, the right being greater in diameter than the left. She was unresponsive to commands and had bilaterally upward plantar responses.

She died 5 hours later, 36 hours after the initial neurologic event and 15 hours after the second neurologic event.

HISTOLOGIC FINDINGS

An autopsy was performed 20 hours after death. There was hemorrhage of the inferior surface of the cerebellum consistent with the second vascular event, and areas of infarction (Fig 2) consistent with the distribution of the AICA. A representative brain stem section was obtained and fixed in 10% formalin for microscopic evaluation. The temporal bones were removed and placed in 20% formalin.

The representative brain stem specimen was embedded in paraffin, sectioned, and stained with Klüver and Barrera stain. The temporal bones were decalcified, embedded in celloidin, and serially sectioned at 20 μm. Every tenth section was stained with H & E.

The structures present in the brain stem section (Fig 3) included the following:

1. Superior vestibular nucleus.
2. Medial vestibular nucleus.
3. Hook fibers of nerve VII.
4. Nuclei of nerve V.
5. Corticospinal tract.
6. Brachium conjunctivum.
7. Restiform body and middle cerebellar peduncle.
8. Trapezoid body.
9. Medial lemniscus.
10. Area of lateral lemniscus.
11. Nucleus of nerve VI.

In this available section all but two of the 11 structures demonstrated damage from the vascular event (Fig 3C). These were the corticospinal tract and the brachium conjunctivum.

RIGHT EAR

External and Middle Ear. The external auditory canal and the tympanic membrane were normal. The structures of the middle ear were normal except for the round window niche, which was partially filled with extravasated blood. In this area the mucosa showed engorged blood vessels and extravasated blood. The epithelial layer of the mucosa was broken at this level. The labyrinthine capsule appeared normal.

Internal Meatus. Several collections of extravasated blood were present in the subarachnoid space along the internal auditory meatus (Fig 4). Collections of inflammatory cells were present mainly around the vestibular nerve at the level of Scarpa's ganglion and around the auditory nerve at the base of the modiolus. Several degenerated blood clots lo-

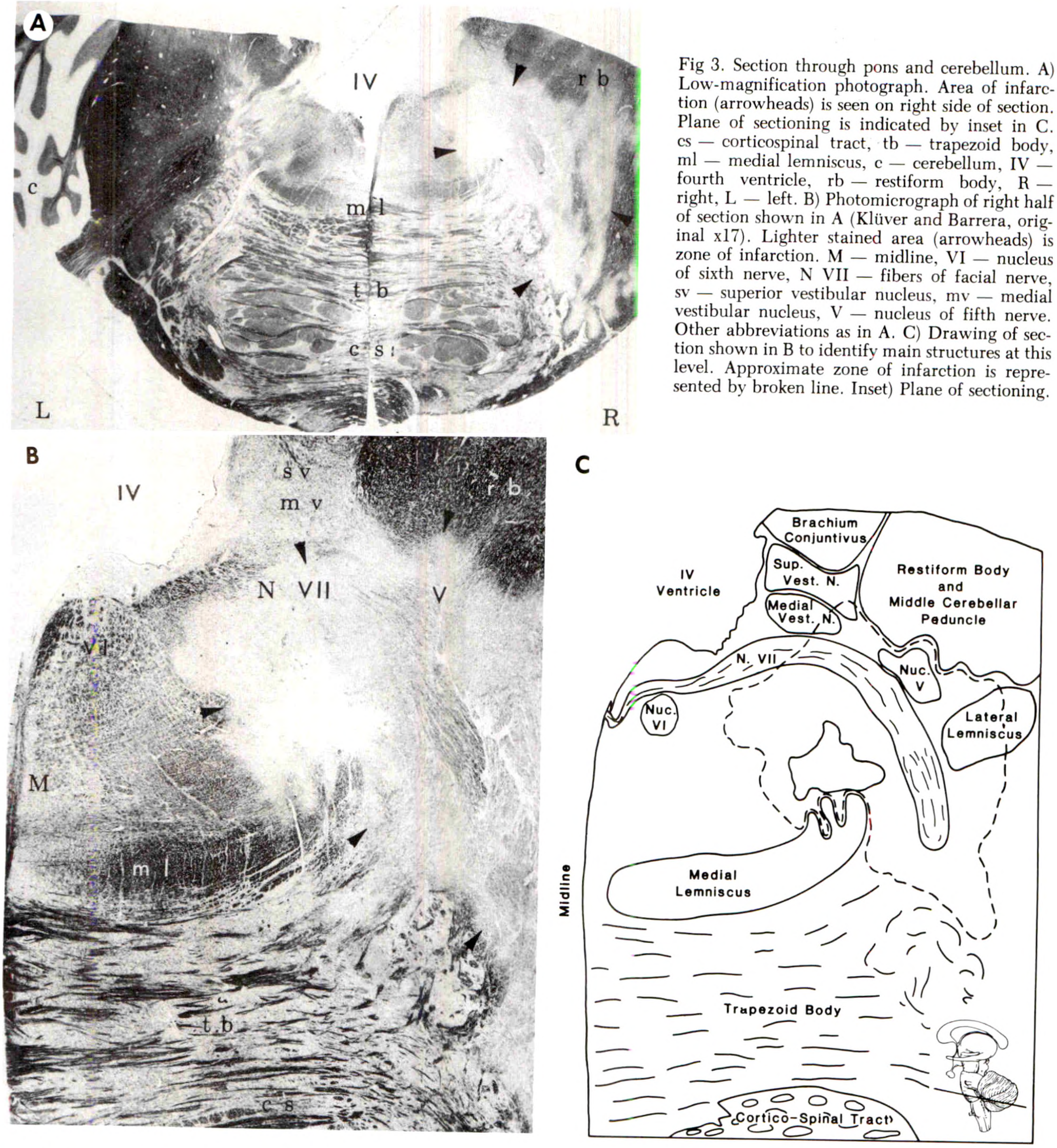

Fig 3. Section through pons and cerebellum. A) Low-magnification photograph. Area of infarction (arrowheads) is seen on right side of section. Plane of sectioning is indicated by inset in C. cs — corticospinal tract, tb — trapezoid body, ml — medial lemniscus, c — cerebellum, IV — fourth ventricle, rb — restiform body, R — right, L — left. B) Photomicrograph of right half of section shown in A (Klüver and Barrera, original x17). Lighter stained area (arrowheads) is zone of infarction. M — midline, VI — nucleus of sixth nerve, N VII — fibers of facial nerve, sv — superior vestibular nucleus, mv — medial vestibular nucleus, V — nucleus of fifth nerve. Other abbreviations as in A. C) Drawing of section shown in B to identify main structures at this level. Approximate zone of infarction is represented by broken line. Inset) Plane of sectioning.

cated at the medial portion of the meatus were surrounding the cochlear and vestibular nerves and were beginning to be organized. Early blood vessels could be recognized within the clots. The lumen of the labyrinthine artery was empty for most of its length.

Auditory Nerve. The auditory nerve fibers at the fundus of the meatus were surrounded by fluid that contained some inflammatory cells. The fluid and the inflammatory cells did not penetrate the cribriform openings (Fig 4A). The rest of the auditory nerve showed little change, except for perineural infiltration with inflammatory cells.

Facial Nerve. The perineural space of the facial nerve was infiltrated by inflammatory cells up to the level of the genu. In some areas along the nerve, the fibers were separated by a mild infiltration of inflammatory cells and by some congested blood vessels (Fig 4B).

Cochlea. The blood vessels of the modiolus appeared congested. Some showed thrombus formation (Fig 4C). The cytoplasm of the spiral ganglion cells lost the Nissl substance and became finely granular in appearance. Large vacuolar spaces developed between the cells and the myelin sheath surrounding them. The nucleus stained darker than

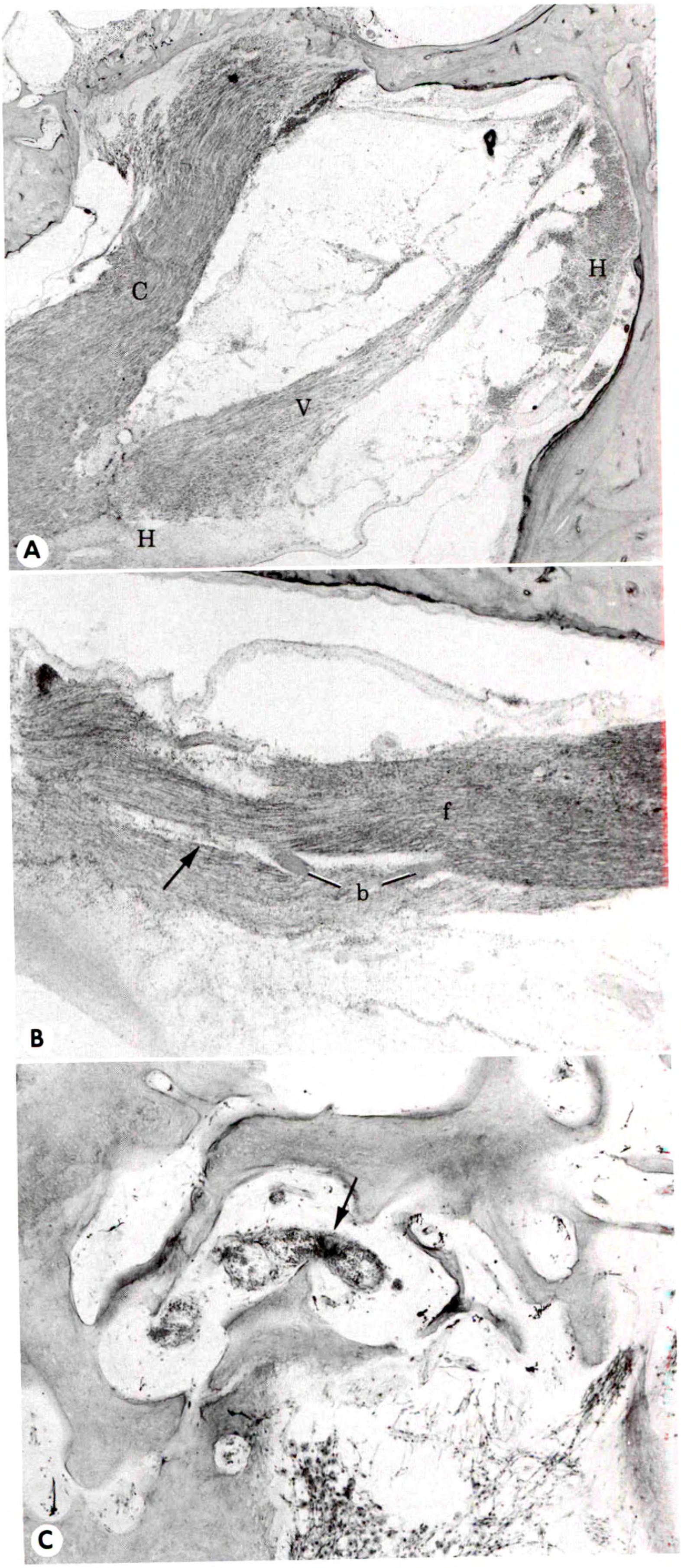

Fig 4. Right ear. A) Internal auditory meatus, showing cochlear nerve (C), inferior branch of vestibular nerve (V), and hematoma (H) surrounding nerves (original x26). B) Facial nerve (f), showing mild infiltration of inflammatory cells (arrow) (original x48). b — congested blood vessels. C) Portion of modiolus, showing thrombosed blood vessel (arrow) (original x80).

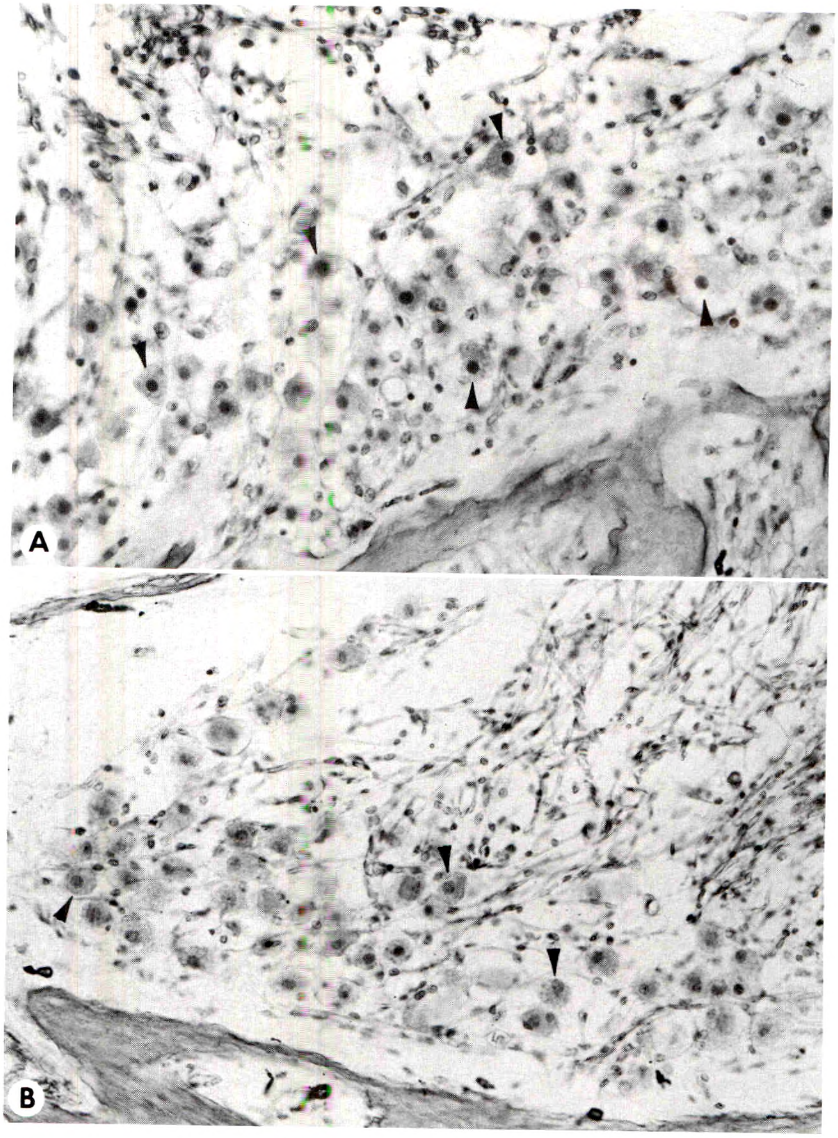

Fig 5. Cochlear ganglion cells (arrowheads) at basal turn of cochlea. A) Right ear (original x325). Cells are degenerating. B) Left ear (original x260). Cells show mild postmortem changes.

the cytoplasm and became finely granular without a recognizable nucleolus (Fig 5A). The cells of the stria vascularis were in different stages of degeneration. Cellular debris was accumulated near the strial surface (Fig 6A).

The cochlear reconstruction showed that most of the outer hair cells of the organ of Corti had degenerated throughout the labyrinth (Figs 7A and 8). The inner hair cells, however, remained intact, with the exception of the first 9 mm of the basal turn (Fig 8). Cellular debris was accumulated on the endolymphatic surface of the organ of Corti. The inner and outer sulcus cells showed mild degenerative changes. The tectorial membrane remained intact (Fig 7A). The basilar membrane also remained intact. There was a finely granular proteinaceous precipitate in the perilymph and to a lesser degree in the endolymph. A collection of inflammatory cells was present in the scala tympani at the level of the round window, where a finely fibrillar material was attached to the perilymphatic surface of the round window membrane. The cochlear aqueduct contained extravasated blood in its entire length, including the openings at the scala tympani and at the posterior fossa.

Vestibular System. The endolymphatic space of the semicircular canals and the utricle contained a finely granular proteinaceous precipitate. In contrast, the endolymphatic space of the sacculus as well as the lumen of the endolymphatic duct and sac were free of precipitates. The perilymphatic space contained a finely granular proteinaceous precipitate that was more concentrated at the level of the perilymphatic cisterna. The epithelium of the cristae showed large vacuoles. Many sensory cells had disintegrated. The supporting cells still could be recognized (Fig 9A). These changes seem to be more advanced in the posterior canal crista (Fig 10A). Cellular debris was accumulated at the surface of the epithelium between the crista and the cupula. The cupula was well preserved in all canals.

The epithelial layer of the macula of the saccule was disintegrated. Cellular debris had accumulated

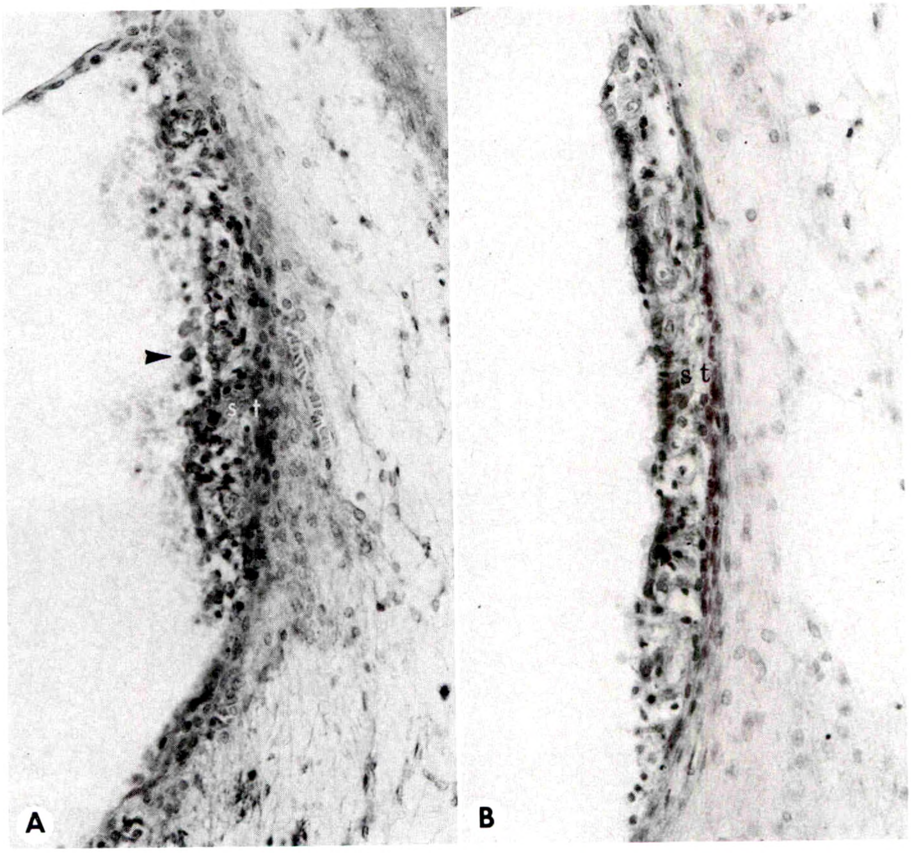

Fig 6. Stria vascularis (st) at basal turn of cochlea (original x260). A) Right ear. Cellular debris is accumulating at strial surface (arrowhead). B) Left ear, showing mild postmortem changes.

beneath the otolithic membrane. The latter was detached and almost completely degenerated (Fig 11A).

The macula of the utricle showed large vacuolar spaces. Small numbers of sensory and supporting cells could be recognized. The otolithic membrane was detached, and cellular debris had accumulated in the subotolithic space (Fig 12A).

Vestibular Nerve. The perineural space of the vestibular nerve was infiltrated by large numbers of inflammatory cells and fibrinoid material (Fig 4A). Large numbers of inflammatory cells infiltrated the vestibular nerve, separating individual nerve fibers as well as Scarpa's ganglion cells (Fig 13). The ganglion cells showed degenerative changes consisting of loss of Nissl substance in the cytoplasm, clear spaces separating the cell bodies from the myelin sheath, and pyknotic changes in the nucleus (Fig 14A).

LEFT EAR

External and Middle Ear. The external auditory canal, the tympanic membrane, the middle ear spaces, and the ossicular chain were normal.

Internal Meatus. The internal auditory meatus and the cochlear, vestibular, and facial nerves were normal.

Cochlea. The organ of Corti showed moderate postmortem changes (Fig 7B). The reconstruction of the cochlea showed that the inner hair cells were degenerated in the first 3 mm. The outer hair cells were totally degenerated in the first 4 mm and partially degenerated (25% to 75%) up to the 17-mm mark. There was a patchy degeneration in the rest of the cochlea (Fig 15). The stria vascularis showed spotty degeneration mainly in the upper second and third turns. The strial cells showed mild postmortem degeneration (Fig 6B). The spiral ganglion cells also showed mild postmortem degeneration (Fig 5B).

Vestibule. The epithelium of the cristae of the semicircular canals showed moderate postmortem degeneration. Large vacuoles were seen in the epithelium. Some sensory cells still could be recognized, as well as most of the supporting cells (Fig 9B). The postmortem degeneration seemed to be more advanced in the crista of the posterior canal (Fig 10B). The cupula was well preserved in all the canals. The macula of the saccule showed moderate to advanced postmortem changes. The epithelium contained many disintegrated sensory and supporting cells. The otolithic membrane was detached from the epithelium (Fig 11B). Similar changes were found in the macula of the utricle (Fig 12B). The Scarpa's ganglion cells showed mild postmortem changes (Fig 14B).

DISCUSSION

The specimens herein reported represent changes that occurred during the first 36 hours after the vas-

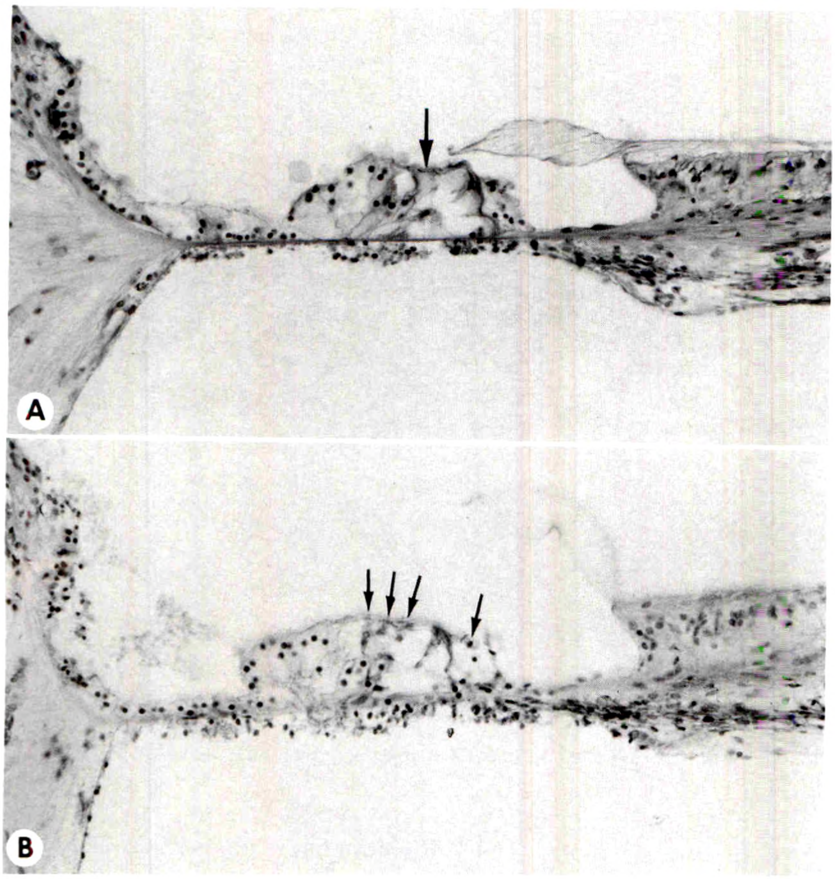

Fig 7. Organ of Corti of basal turn (original x195). A) Right ear, showing loss of outer hair cells (arrow). B) Left ear. Inner and outer hair cells can be recognized (arrows).

cular accident. The findings allow correlation of the structural damage with the defined criteria necessary for diagnosis of an AICA thrombosis, and give evidence of the extent of damage that occurs to the peripheral organ.

The sudden right unilateral hearing loss experienced by this patient is difficult to explain on the basis of a brain stem (cochlear nucleus, trapezoid body, superior olivary nucleus) injury, in that bilateral effects or only distortion of sound would be caused by these lesions. This suggests that the sudden loss of hearing on the right, ipsilateral side may have been due to a peripheral cochlear or eighth nerve event.

The sudden onset of vertigo can be accounted for by involvement of the vestibular nuclei. Indeed, the spontaneous vertical rotatory nystagmus observed 12 hours after onset of symptoms suggests that involvement. On the other hand, because of the probable peripheral cochlear loss of function occurring at the time of vestibular symptoms, a peripheral vestibular event is more likely.

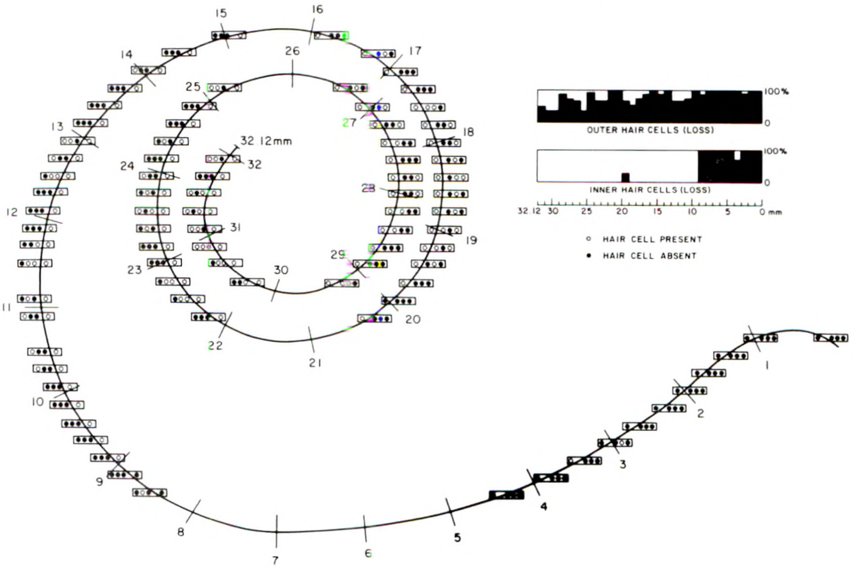

Fig 8. Reconstruction of cochlea of right ear. Bar graphs show percentage of sensory cell degeneration. Most of outer hair cells have degenerated throughout cochlea. Inner hair cells are degenerated only in first 9 mm.

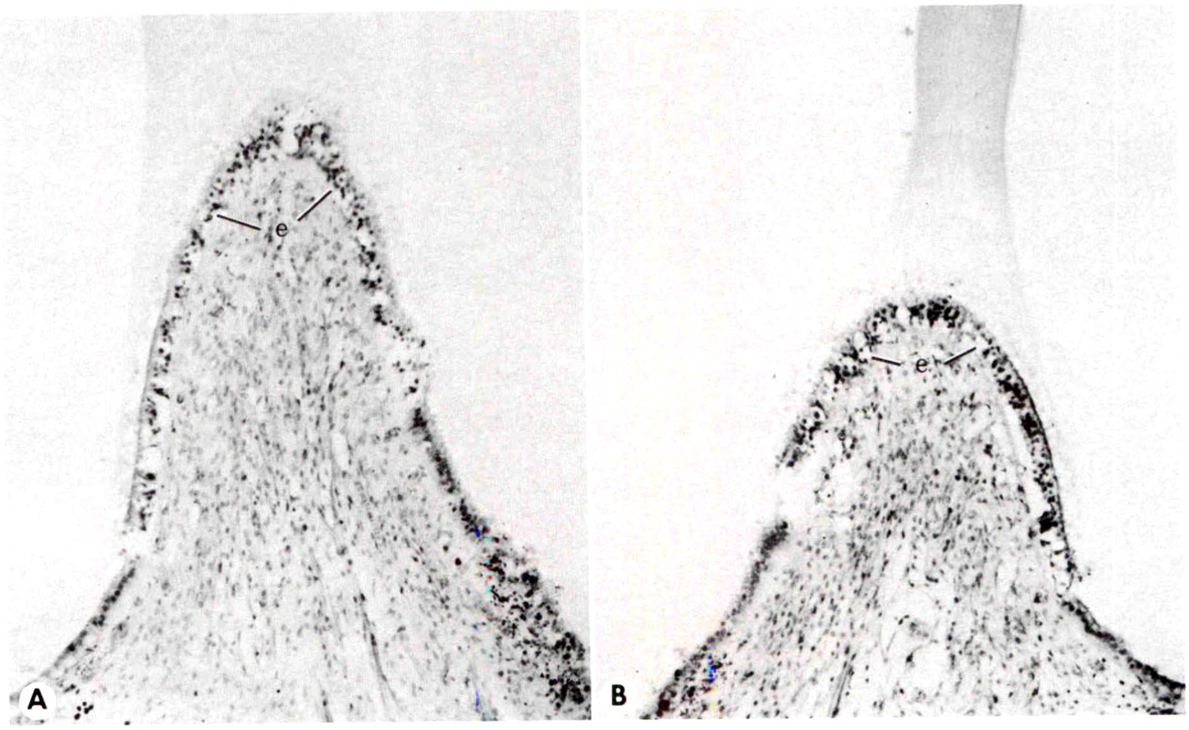

Fig 9. Crista of lateral semicircular canal ampulla, showing moderate postmortem changes in epithelium (e) (original x150). A) Right ear. B) Left ear.

The characteristics of AICA thrombosis (early vestibular signs and symptoms and early appearance of loss of hearing[2] followed by other neurologic events) suggest that these earliest otologic signs and symptoms may be due to changes in the peripheral organ. The histopathologic changes of the labyrinth involving the pars superior and pars inferior support this conclusion, accounting for the rapid onset of both vestibular and auditory symptoms and signs.

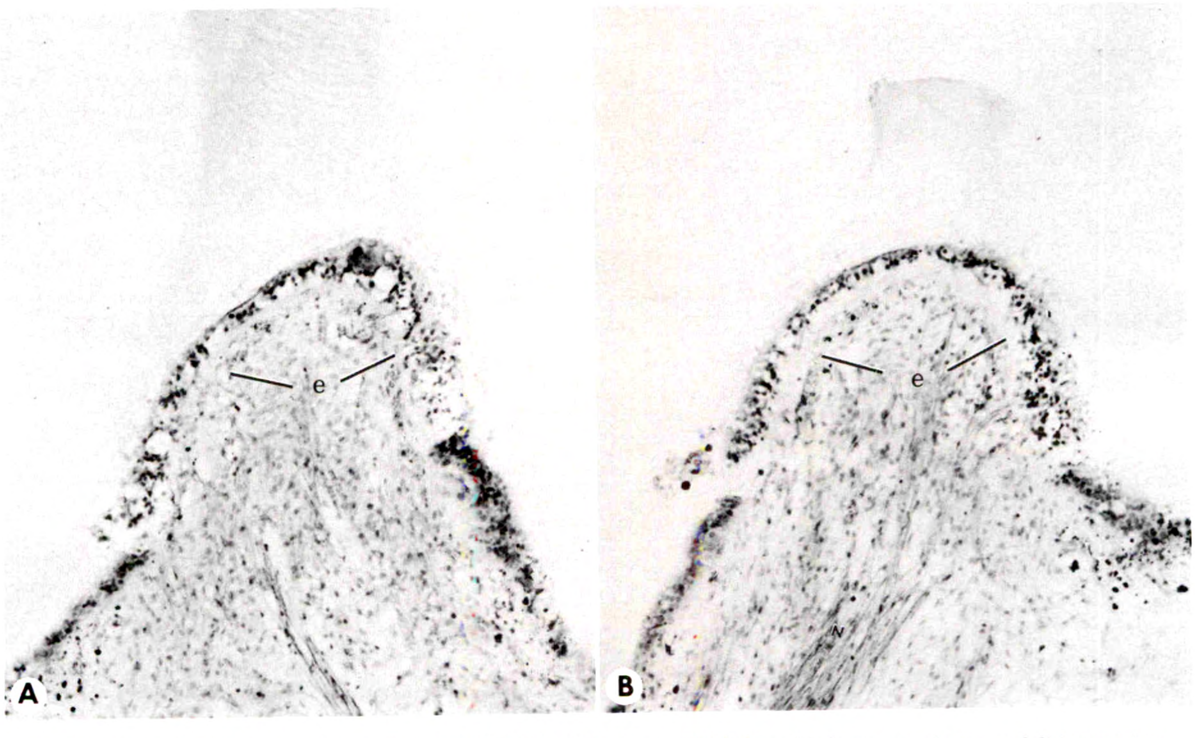

Fig 10. Crista of posterior canal ampulla (original x150). A) Right ear. Epithelium (e) shows vacuolation and disintegration of sensory cells. B) Left ear. Partial disintegration of epithelium (e) is less marked than in A.

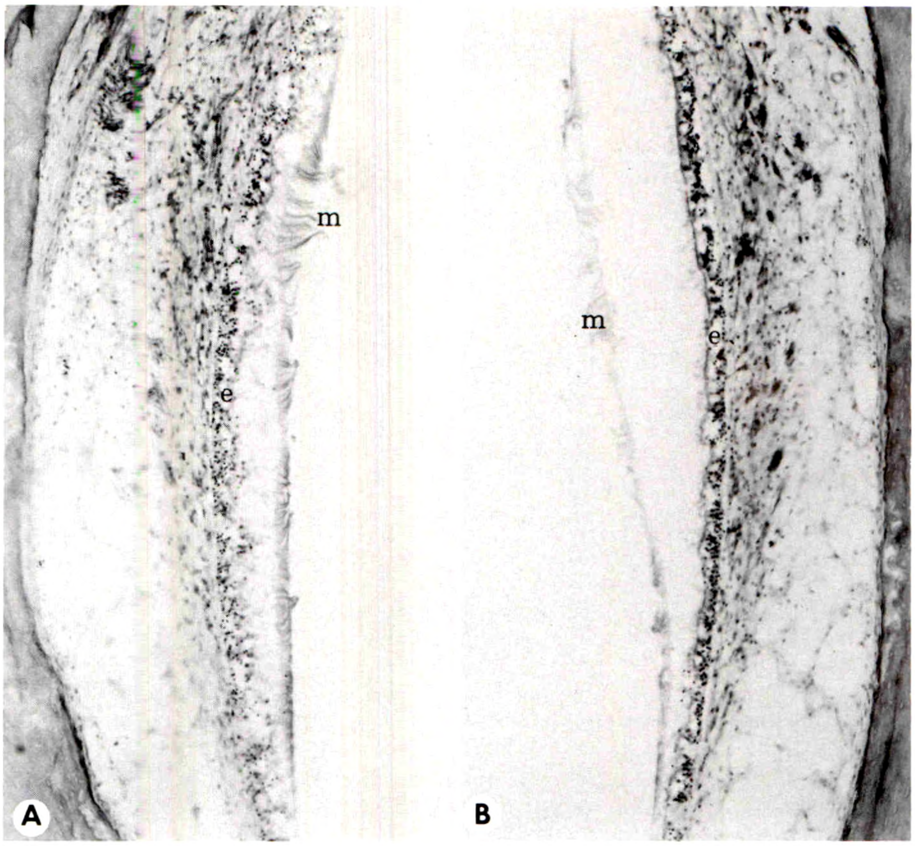

Fig 11. Macula of saccule (original x97). A) Right ear, showing advanced disintegration of epithelial layer (e) and detachment of otolithic membrane (m). B) Left ear, showing postmortem changes in epithelium (e) and detachment of otolithic membrane (m).

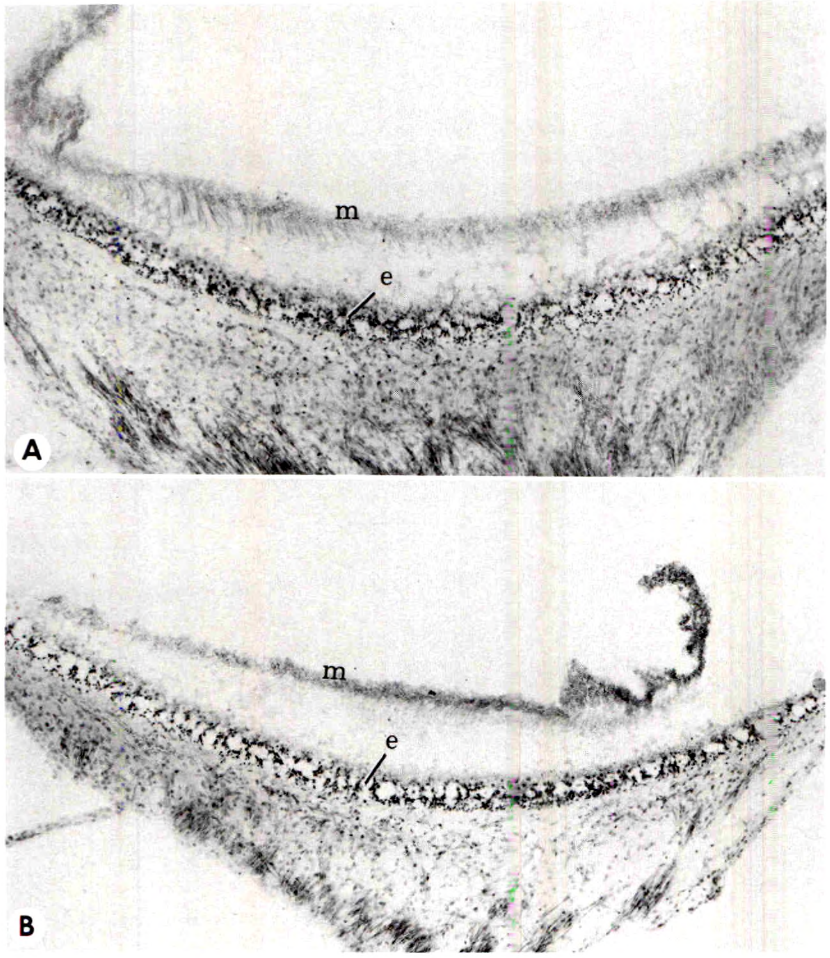

Fig 12. Macula of utricle, showing postmortem changes in epithelium (e) and detachment of otolithic membrane (m) (original x97). A) Right ear. B) Left ear.

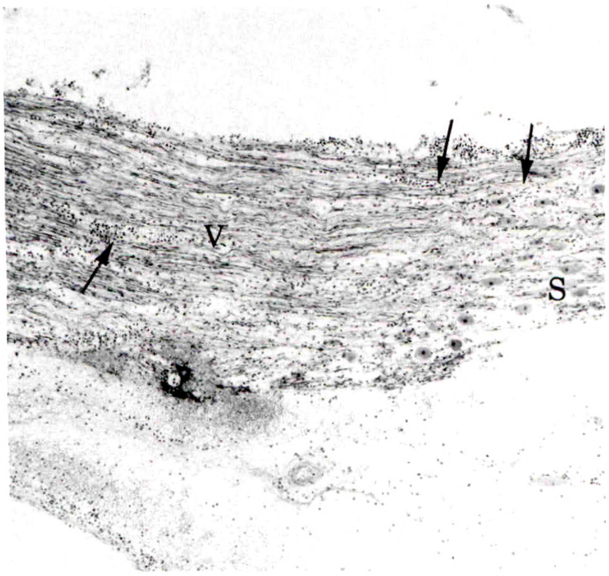

Fig 13. Vestibular nerve (V) and Scarpa's ganglion cells (S) of right ear, infiltrated by inflammatory cells (arrows) (original x75).

On the basis of the damaged brain stem structures (Fig 3), if the patient had survived, certain neurologic deficits could have been predicted. These can be compared to the deficits identified clinically during the patient's illness.

1. Superior vestibular nucleus: vertical nystagmus.
2. Medial vestibular nucleus: vertical nystagmus.
3. Hook fibers of nerve VII: complete facial paralysis on right.
4. Nucleus of sensory nerve V: anesthesia of right side of face.
5. Nucleus of motor nerve V: masseter weakness on right.
6. Pons (lateral portion): disturbances of impulses from cerebral cortex to contralateral cerebellum; distortion of accuracy and smoothness and purposeful movement.
7. Trapezoid body (principal pathway from central cochlear nucleus to cortex): central disorder of hearing; distortion of signals to opposite cortex, causing interpretive clinical hearing symptoms but not sudden hearing loss.
8. Medial lemniscus: kinesthetic and tactile abnormalities of opposite side of body.
9. Restiform body: loss of modulation of vestibular impulses by cerebellum; gross dysequilibrium and vertigo.
10. Right nucleus of nerve VI: right lateral rectus palsy.
11. Lateral pontine nuclei (receives fibers from superior colliculus): visual distortion.
12. Lateral lemniscus (cochlear nucleus/cortex pathway): distortion of perception of sound, ipsilateral cortex (possible distortion of perceived music).

Therefore, the symmetric hearing loss found a year before admission could account for the loss of sensory cells of the organ of Corti and possible partial neural degeneration of the left ear.

In the right ear, postmortem degeneration alone does not account for the degenerative cytologic changes observed in the organ of Corti, stria vascularis, spiral ganglion cells, macula of the saccule, and Scarpa's ganglion cells. These changes are consistent with a partial or total obstruction of the arterial circulation.

The hearing loss noticed by the patient after the first neurologic episode can be accounted for by the almost complete degeneration of the outer hair cells as well as the inner hair cell degeneration at the basal end of the right cochlea.

Likewise, although one cannot exclude the effect of the brain stem lesions, a significant component to

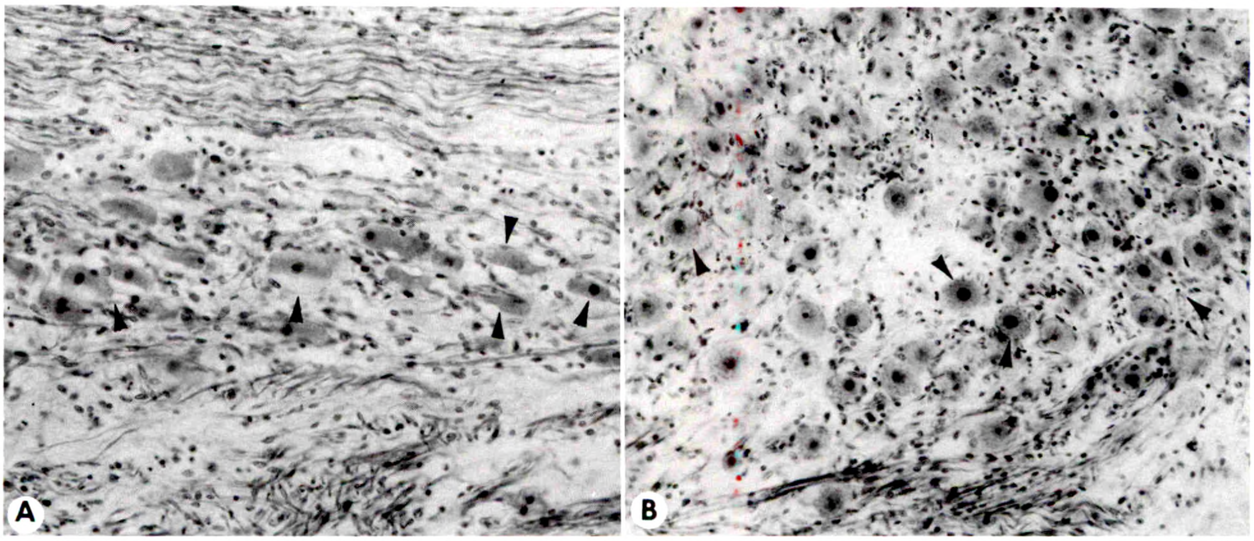

Fig 14. Cells of Scarpa's ganglion (original x200). A) Right ear, showing degenerative changes. Notice large vacuolar spaces between cell bodies and myelin sheath (arrowheads). B) Left ear, showing mild postmortem changes (arrowheads).

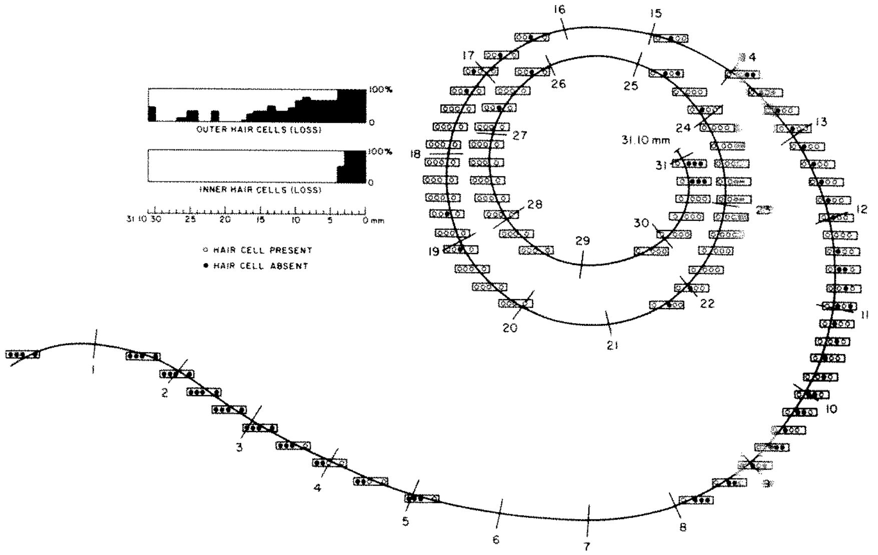

Fig 15. Reconstruction of cochlea of left ear. Degeneration of inner and outer hair cells is less extensive than in opposite ear (see Fig 8).

the initial vestibular symptoms can be accounted for by the degeneration of the sensory epithelial elements and the degeneration of Scarpa's ganglion cells.

The literature suggests that patients who have suffered from AICA thrombosis rarely die from the event. The temporal bone findings of this case suggest that there would have been a permanent change of the peripheral organ and permanent central disorders of hearing, balance, tactile sense, and vision. These permanent changes should be identifiable and separable by means of an array of modern testing methods. The herein-defined central and peripheral histopathologic changes should allow accurate correlation of these test results with the predicted lesions. This suggests a need for physiologic and histopathologic studies of the CNS structures and peripheral organs from long-term survivors of AICA thrombosis.

It is likely that the sudden loss of hearing and balance in patients with AICA thrombosis is initially due to involvement of the peripheral organ, followed shortly by other signs and symptoms attributable to the damage to CNS structures.

These changes due to AICA thrombosis of the peripheral organ are similar to but less dramatic than those produced in experimental total AICA occlusion in guinea pigs, which demonstrated total degeneration of the organ of Corti at 17 hours postocclusion.[3] With partial experimental obstruction, only external hair cells were lost; this finding is similar to those in this patient.[4] The changes are also similar to but less severe than the changes in Reye's syndrome, in which venous congestion impairs circulation.[5] In Reye's syndrome, hearing loss and balance disorders are evidenced only by histologic data because of the concomitant severe neurologic events.

SUMMARY

1. This is the first reported human temporal bone injury from a documented arterial occlusion.
2. It is likely that the hearing loss in AICA occlusion is due to injury of the cochlea.
3. The vestibular symptoms may have been due to central injuries in addition to the injury of the labyrinth.
4. Pathologic changes of the cochlea and the vestibular apparatus are similar to those from experimental AICA occlusion in animals and those due to venous congestion in Reye's syndrome.
5. There is need for a temporal bone and brain stem study from a long-term survivor of AICA occlusion.
6. Clinical diagnoses of vascular causes for disorders of hearing and balance are common. Supporting objective data for these diagnoses are almost nonexistent.

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ASSOCIATE EDITOR'S COMMENTS

This is an important contribution to the literature, because it documents both the central and peripheral histopathologic changes following anterior inferior cerebellar artery thrombosis. However, this editor and some of the reviewers disagree with the authors' contention that the patient's vestibular and auditory symptoms are primarily due to vascular effects on the end organs, rather than the CNS effects.

The reviewers felt that many of the changes in the temporal bone represented postmortem autolysis, and one felt that the purported thrombosis of the vessel in the modiolus shown in Fig 4C actually represented a tangential cut through the wall of the vessel, rather than a clot. That reviewer also indicated, "It is very common for postmortem autolysis to be at different stages in the two ears of the same individual even though other parameters such as refrigeration, time of removal, etc., remain constant."

The authors contend that the sudden right unilateral hearing loss is difficult to explain on the basis of brain stem injury, since bilateral effects or only distortion of sound would result from such lesions in the brain stem. This is not always the case. Daugherty et al[1] reported nine patients with hearing loss from multiple sclerosis, seven of whom had only a unilateral loss. In nearly all, the hearing impairment was acute, and improvement subsequently occurred in all but two. Several other case reports document similar findings. Multiple sclerosis does not involve either the end organ or the vascular supply to it. Rubenstein et al,[2] discussing cerebellar infarction as a cause of vertigo, related a case of an acute right cerebellar hemisphere infarction with surrounding edema that exhibited signs and symptoms that included a near-total unilateral right sensorineural hearing loss. The patient recovered over the subsequent few weeks, and audiometry 8 months later showed near-normal hearing in the right ear. If the hearing loss in that patient was due to end organ infarction, recovery should not have occurred. It seems more likely that CNS events were responsible for the unilateral sensorineural hearing loss. The widely held belief that CNS lesions cannot cause unilateral hearing loss is no longer appropriate.

This editor's interpretation of this article is that the findings unequivocally demonstrate central vestibular and auditory findings that can explain the patient's symptoms and clinical course. The histopathologic findings in the end organs may or may not reflect a vascular ischemia and may or may not have contributed to the clinical course of the patient.

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Associate Editor

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PREVENTION OF ASPIRATION IN INFANTS AND YOUNG CHILDREN: FEDERAL REGULATIONS

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Aspiration of and asphyxiation from small objects is a well-known danger to young infants and children. At present, there are three different federal regulations that address this problem, by specifying different dimensions of height, width, and length. The Small Parts Regulation, which affects toy size, is the least stringent and is being challenged. The anatomic and physiologic concepts behind these important regulations are analyzed and discussed. The idea of a single generic standard is also reviewed.

KEY WORDS — asphyxiation, aspiration, children.

INTRODUCTION

Choking and aspiration of small objects by children has been a well-recognized cause of significant morbidity and even death for centuries. During the last 50 years, skilled endoscopists have been able to remove ingested foreign bodies relatively safely, and have reduced dramatically the associated mortality from such unfortunate events.[1] However, despite physicians' developing these surgical skills and their heroic efforts, prevention remains the benchmark to measure further improvements in childhood safety.

In 1979, the Consumer Product Safety Commission[2] issued regulations under provisions of the Federal Hazardous Substance Act to ban certain toys and other articles that are intended for children under 3 years of age and that present unreasonable risks of injury because of small parts. Those regulations are codified and intended to address risks of death and injury from asphyxiation, aspiration, or soft tissue wounds (see Table).

The testing procedure used to determine if a toy or article intended for children under 3 years of age should be banned because of small parts is based upon the ability of the object to fit entirely into a truncated cylinder. This cylinder has an interior diameter of 31.7 mm (1.25 in), a minimum interior depth of 25.4 mm (1.0 in), and a maximum interior depth of 57.1 mm (2.25 in) (Fig 1). The product to be tested must be placed into the test cylinder and must be large enough *not* to fit entirely within the cylinder. Any detachable component of a toy is tested in the same manner.

This small parts cylinder, in conjunction with additional regulations for rattles and pacifiers, has reduced the number of choking episodes observed in children over these last 10 years.

However, a review by the Consumer Products Safety Commission[3(pp7-9)] staff of choking incidents that occurred between 1973 and 1983 identified 195 choking incidents by children 3 months to 4 years of age on items that were large enough to pass this small parts cylinder test. Indeed, 37 children died as a result of these choking incidents. Spherical objects were identified as the culprit in 66% (112/170) of the incidents.[3(pp7-9)]

This same study identified 71 choking incidents, including 14 deaths and 1 case of brain damage, for products that complied with both existing mandatory and voluntary standards, as well as newer regulations for rattles and pacifiers. Therefore, it is reasonable to surmise that the present standard for small parts is perhaps not sufficiently stringent.

Most recently, in 1986-1987, there were 113,000 incidents of toy-related injuries.[4] About 1.5% were serious enough to require hospitalization. Deaths occurred in 52 children, and approximately two thirds died of asphyxiation. Balloons, balls, small parts, and crib injuries were most often identified.

This apparent laxity in the regulation of small parts has prompted several challenges to the Consumer Products Safety Commission to tighten standards for small parts.[5] An understanding of this problem is important for all physicians, particularly

COMPARISON OF FEDERAL PROTECTIVE GOALS FOR INFANTS AND YOUNG CHILDREN LESS THAN 3 YEARS OF AGE

	Federal Regulations		
Goals	*Small Parts*	*Pacifier*	*Rattle*
Asphyxiation from lodgment of object in throat (pharynx)	No	Yes	Yes
Asphyxiation from obstruction of airway (larynx and trachea)	Yes	Yes	Yes
Aspiration of object into bronchus and lung	Yes	Yes	Yes
Cuts or penetration wounds from pointed objects	No	Yes	Yes

From Federal Regulation 16 CFR 1500.18(a).

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Presented at the meeting of the American Broncho-Esophagological Association, San Francisco, California, April 3-4, 1989.

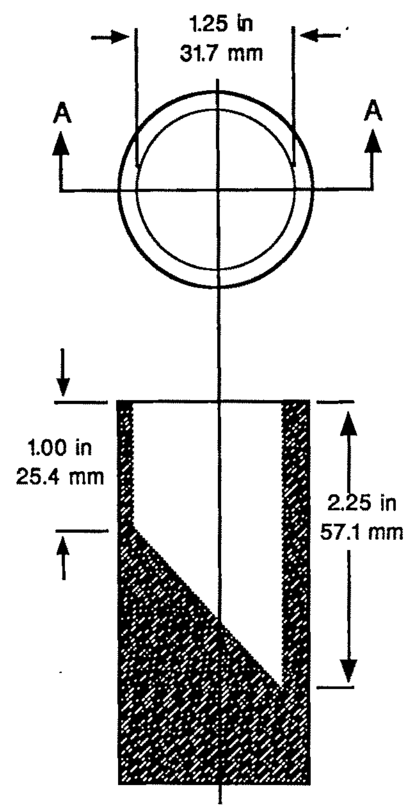

Fig 1. Small part test fixture. Each toy or toy part must not fit completely within cylinder. (Redrawn from Federal Regulation 16 CFR, Part 1501.)

bronchoesophagologists, so that they may be informed, as well as participate in promoting safety legislation for young children.

STRATEGIES FOR PREVENTION

By about 4 months of age, most infants develop sufficient motor skills to bring objects to their mouths and to suck on them. By 6 months of age, these infants also begin to investigate their environment and often place objects into their mouths and gum objects in an attempt to relieve teething pains. Many infants and young children continue this pattern of behavior indiscriminately until they are about 3 years old. Children under 3 years of age are not able to discriminate objects that are potentially dangerous from food that can be eaten and safely swallowed.[3(pp6–10)]

Infants and young children are also not able to easily remove objects from their own throat or mouth in a reasonable fashion. Death is a most tragic outcome and results from obstruction and asphyxiation from blockage of the throat and/or airway (see Table). Morbidity generally occurs from aspiration or partial blockage of the trachea, bronchus, or lung or from a cut or penetrating wound to the pharynx, larynx, or trachea. It is apparent that the most serious injuries arise from blockage of these first two areas (throat and airway), and prevention of this is of paramount importance.

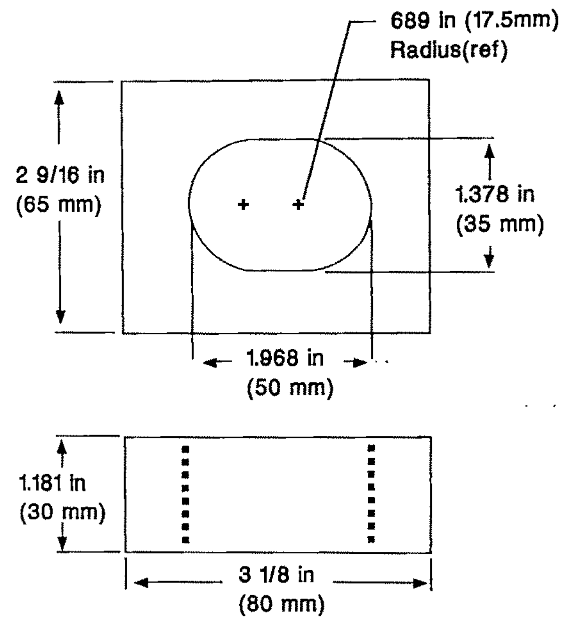

Fig 2. Rattle test fixture. Rattle must pass specifications for minimal width and length. (Redrawn from Federal Regulation 16 CFR, Part 1510.)

The original truncated-cylinder model was based on concepts of anatomic size of the larynx and trachea. This resulted in the selection of a small parts measurement diameter of 31.7 mm (1.25 in). It did not address the problem of the shape of the object or the problem of asphyxiation from penetration to the throat. Most importantly, the truncated cylinder permits passage of the small parts by "either diameter or length." Hence, the diameter, which determines the shape of an object, can be completely ignored if adequate length is achieved. Length of an object has little importance in preventing asphyxiation, but is perhaps meaningful in preventing aspiration. The length (57.1 mm or 2.25 in) is based upon data related to straight pin aspiration and injury.

Strategies for prevention of aspiration can also be based on studies of the physiology of swallowing. An understanding of the different phases of swallowing is very important.[6]

Foreign objects and food that are in the anterior portion of the oral cavity are under voluntary control; as the tongue manipulates the bolus, it will pass posteriorly into the pharynx. Then, swallowing enters the involuntary phase of deglutition. The pharynx and larynx are controlled by the brain stem through the glossopharyngeal and vagus nerves. These control very basic, primitive reflexes that initiate both swallowing and protective gagging. All objects that pass into the pharynx initiate this involuntary phase and must be swallowed or vomited. Children less than 3 years of age are not experienced enough and lack the knowledge to control what they put into their oral cavity voluntarily. We can protect them best by preventing small objects from

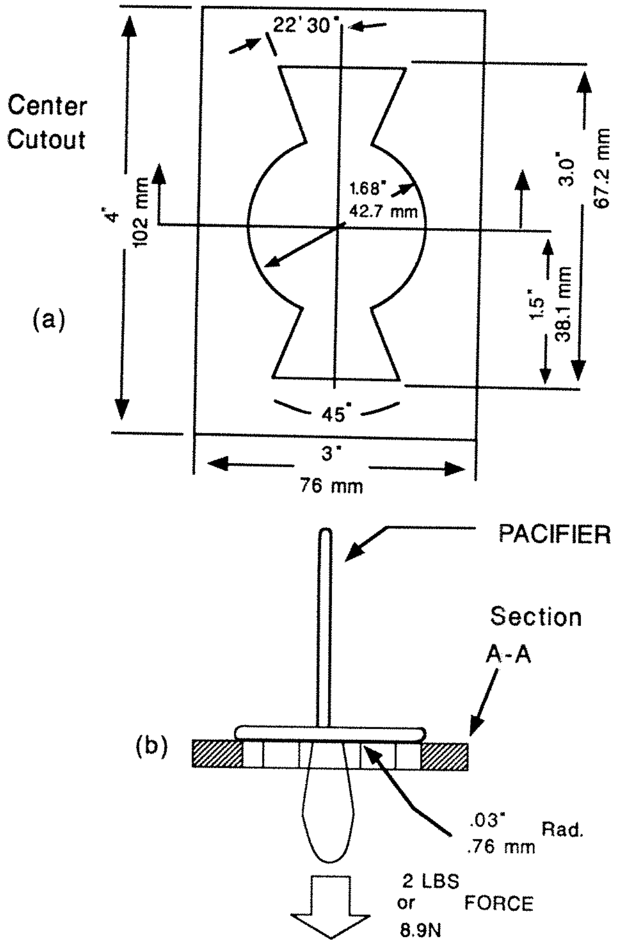

Fig 3. Pacifier test fixture. Pacifier must have both minimal diameter and maximal length. Nipple must withstand 8.9 ng (2 lb) force. (Redrawn from Federal Regulation 16 CFR, Part 1511.)

easily entering the mouth.

The most logical and effective concept is to select standards that prevent penetration into the oral cavity and possible subsequent asphyxiation and/or injuries, that is, to prevent injury. Fortunately, there already exist two standards that appear to meet these needs. These include the rattle regulation, 16 CFR, Part 1510 (Fig 2), and the pacifier regulation, 16 CFR, Part 1511 (Fig 3). These two test fixtures specify both diameter and length. Neither permits disregard of the diameter of the object, and both are designed to prevent penetration to the pharynx through the oral cavity so that objects cannot enter the involuntary phase of swallowing.

Since the population of children less than 3 years of age is at risk of death from asphyxiation from all three types of objects (small parts, rattles, and pacifiers), it is logical that a less rigid, inferior standard should not be accepted for small parts. The accepted standard should apply to all small objects and it should be based upon adequate sampling of factors related to human choking and injury.

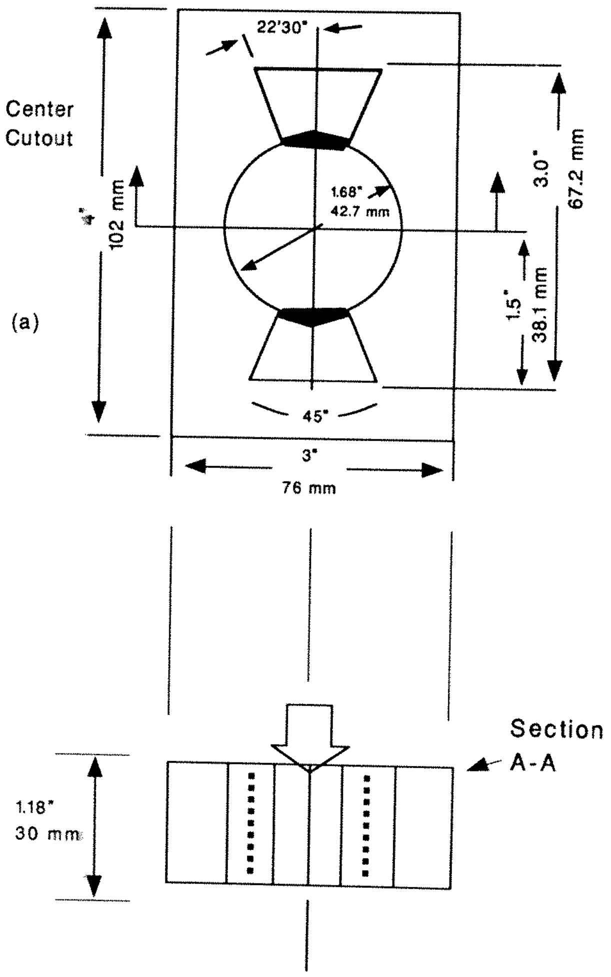

Fig 4. Proposed generic test fixture for pacifiers, rattles, and small parts. (Redrawn with permission from Deppa.[3])

The Consumer Products Safety Commission Internal Report has suggested a generic standard that could be applied to all objects to which young children are exposed. This test device is 42.7 mm (1.68 in) in diameter, including a 16.8-mm (0.66-in) extension on both sides. The maximum length of single objects that would pass the standard would be 30 mm (1.18 in) (Fig 4).[3(pp14-15)] This is presently under consideration and may be codified through federal regulations.

Physicians who care for small children and perform endoscopic removal of foreign bodies should compare all objects that are removed to these known standards. Measurements that provide additional data are essential to help evaluate the need to further strengthen this small parts standard.

CONCLUSION

Aspiration of small objects continues to cause morbidity and mortality for infants and small children. This appears to be partially caused by the fact that some small objects can pass the small parts test by either adequate length or diameter. Spherical shapes remain the most dangerous and are a leading cause of asphyxiation and death.

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Ann Otol Rhinol Laryngol 99:1990

NECK DISSECTION FOR LARYNGEAL ADENOID CYSTIC CARCINOMA: IS IT INDICATED?

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The authors report six cases of adenoid cystic carcinoma with a view to evaluating the validity of neck dissection in this tumor. Adenoid cystic carcinoma may invade regional lymph nodes by direct extension, but true embolic lymph node metastases are so rare, if they exist at all, that neck dissection may be considered an overtreatment.

KEY WORDS — adenoid cystic carcinoma, laryngeal tumor, neck dissection.

INTRODUCTION

Adenoid cystic carcinoma of the larynx is a specific variant of adenocarcinoma of the minor salivary glands and constitutes only a very small fraction of all malignant laryngeal neoplasms.[1] To date only about 100 cases have been reported.[2-10]

It generally is accepted that adenoid cystic carcinoma has a remarkable capacity for local recurrence and a proclivity for neural and hematogenous spread. Opinions differ, however, regarding the incidence of lymph node metastases and how they occur, ie, by direct extension of tumor or by embolic spread. This problem particularly pertains to tumors of the major salivary glands, some of which contain a large intraglandular and/or paraglandular component of lymph nodes. The larynx, however, presents a different anatomic situation: this organ has no intrinsic lymph nodes, so that here this controversial problem can be studied.

The question that may now be raised is whether or not neck dissection represents an overtreatment for laryngeal adenoid cystic carcinoma.

MATERIALS AND METHODS

A search through the anatomic pathology files of the last 23 years (1966 to 1988) at the Department of Otolaryngology of the University of Padua and at the Department of Pathology of the Presbyterian University Hospital and Eye and Ear Hospital of Pittsburgh yielded six cases of adenoid cystic carcinoma of the larynx. Paraffin-embedded, H & E–stained microscopic slides of the tumor were available for study on each patient.

RESULTS

The pertinent clinicopathologic data on these six cases are summarized in the Table.

DISCUSSION

There is no consensus of opinion regarding the management of adenoid cystic carcinoma of the larynx,[11] and particularly whether or not neck dissection is indicated.

Valid guidelines are hard to find in the literature, because adenoid cystic carcinomas of the larynx are rare, and reports contain only single cases or small series, treated different ways and often with little or no follow-up. The most important problem initially is in establishing the correct diagnosis, since adenoid cystic carcinoma may be confused with other benign and malignant neoplasms of the larynx such as pleomorphic adenoma, infiltrating salivary duct carcinoma with a cribriform pattern, adenoid squamous cell carcinoma, basaloid squamous cell carcinoma, and mucoepidermoid carcinoma. Sometimes laryngeal neuroendocrine carcinomas may mimic the appearance of adenoid cystic carcinoma, but immunohistochemical and ultrastructural investigations are useful in reaching a correct diagnosis.

Once the diagnosis of laryngeal adenoid cystic carcinoma is established, then staging procedures are important. Evaluation for distant metastases should be carried out in all patients with this tumor. Pretreatment evaluation should include panendoscopy, chest radiography, whole lung tomography, liver echotomography, computed tomography of the brain, bone scintigraphy, and laboratory tests.

Although it is believed that adenoid cystic carcinoma may metastasize to the regional lymph nodes, Ferlito and Caruso[2] were unable to find any well-documented reports of laryngeal adenoid cystic carcinoma with lymph node metastases. Since their review, several papers have been published indicating lymph node metastases, but with no convincing histologic evidence. While there is no reason that this

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Supported by the Laryngeal Cancer Association, Italy.

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SUMMARY OF CLINICOPATHOLOGIC DATA ON SIX PATIENTS WITH ADENOID CYSTIC CARCINOMA OF LARYNX

Patient	Age/Sex	Location	Subtype of Tumor	Metastases Cervical	Metastases Visceral	Invasion	Treatment	Follow-Up	Remarks
1	52/F	Supraglottis	Tubular	None	None		Lateral pharyngotomy and resection of epiglottis	No evidence of disease (11 yr)	
2	29/F	Subglottis	Tubular	None	None		Resection of mass	No evidence of disease (15 yr)	
3	72/F	Subglottis	Solid	None	Liver, bones (multiple)	Thyroid gland	Irradiation of metastases; resection of subglottic area, left cricoid, and upper trachea; left thyroid lobectomy; chemotherapy (no response)	Died of disease (21 mo)	Metastatic deposits were recognized before primary treatment
4	58/F	Subglottis	Solid	None	None	Strap muscles and capsule of left lobe of thyroid	Total laryngectomy, left thyroid lobectomy	Lost	One incidental lymph node was free of tumor
5	48/M	Subglottis	Tubular	None	None	Capsule of thyroid gland	Total laryngectomy, total thyroidectomy and left radical neck dissection plus irradiation	No evidence of disease (38 mo)	66 left cervical lymph nodes were free of tumor
6	76/M	Supraglottis	Solid	None	Lung	Soft tissues	Total pharyngolaryngectomy plus irradiation, chemotherapy (cisplatin)	Alive with disease (31 mo)	Resection margin of surgical specimen was involved by tumor

tumor should not metastasize via the lymphatic system, it actually metastasizes more as a sarcoma than as a carcinoma.

The high incidence of lymph node metastases (with a pooled incidence of 34%) from adenoid cystic carcinoma of the submandibular gland is surprising[12] and seems to confirm that lymph node invasion occurs from direct or contiguous infiltration.[13,14] Lymph node involvement contrasts sharply with frequent blood-borne metastatic spread.[2]

Multiple visceral and osseous metastases, as in our patient 3, may occur in the absence of lymph node metastasis (Fig 1). The fact that cervical lymph nodes are free of metastases cannot, therefore, be considered a favorable prognostic sign in this tumor as it is in squamous cell carcinoma.

Adenoid cystic carcinoma may invade regional lymph nodes by direct extension, but true embolic lymph node metastases are rarely described in laryngeal tumors. Of course this possibility cannot be excluded, but if it does exist, it must be uncommon. I. Friedmann, C. Micheau, and J. Rosai (personal communications, March, September, and July 1988, respectively) have observed no lymph node metastases in their experience with laryngeal adenoid cystic carcinomas.

After diagnosis and staging, it is essential to treat the patient correctly. At present, the treatment of choice remains surgical removal — partial or total

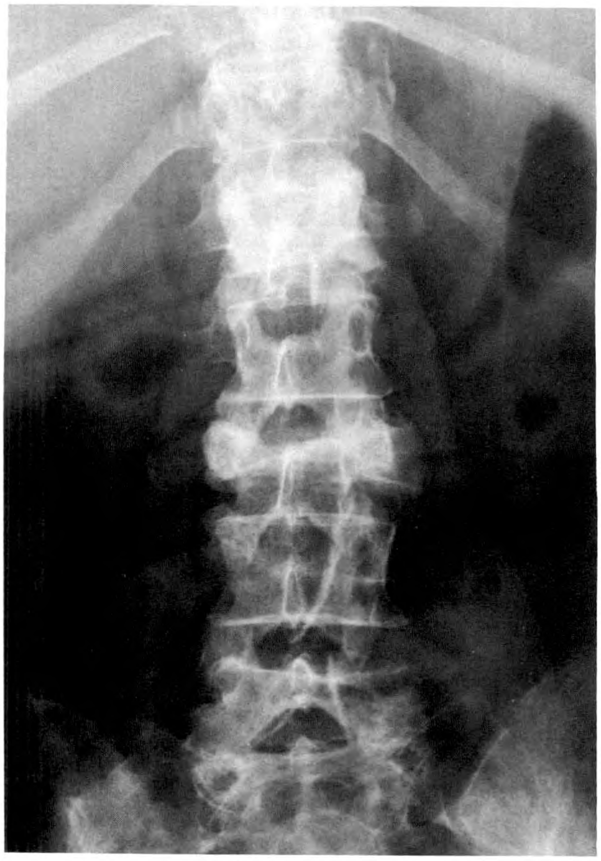

Fig 1. (Patient 3) Adenoid cystic carcinoma with vertebral metastases.

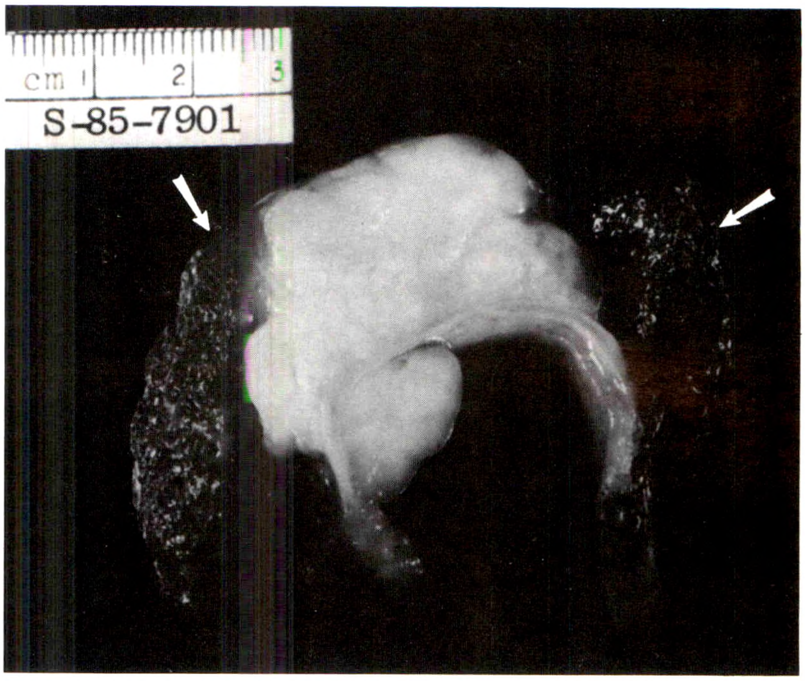

Fig 2. (Patient 5) Horizontal section through subglottic larynx showing adenoid cystic carcinoma with small luminal and much larger extraluminal component. Tumor abuts upon capsule of right and left lobes of thyroid (arrows).

laryngectomy according to the size and location of the neoplasm. This tumor has proved to be radiosensitive but not radiocurable (Figs 2 and 3). Resection of the pharynx and cervical esophagus also may be required for large subglottic tumors. The presence of lung metastases need not prevent surgical extirpation of the primary tumor, since isolated or multiple metastases may remain dormant even for a decade or more. Neck dissection, however, is not indicated unless the patient has clinically enlarged and/or histologically confirmed nodal metastases.

No lymph node metastases were found in any of our six patients, although in patient 6 there was a recurrence in the neck, ie, the persistence of the primary tumor, which could have been misinterpreted as a cervical metastasis.

We agree with Conley and Dingman[13] that for all adenoid cystic carcinomas of the head and neck, "a radical neck dissection is not included in the primary operation unless there is either gross metastasis or there is the necessity of including a large soft tissue cuff."

At present, the role of chemotherapy in the management of this tumor is still undefined.

In this study, patients 1, 2, and 5 were alive and well 11, 15, and about 3 years, respectively, after diagnosis. Patient 3 died of the disease after 21 months, and patient 6 is alive but with disease after 31 months. Patient 4 was lost to follow-up. Our findings imply that histologic subtypes of this tumor may have important prognostic significance, with the solid variant behaving more aggressively (Fig 4). The extent of pretreatment of the tumor also influences prognosis.

The success of treatment and ultimate prognosis, however, cannot be evaluated in terms of 5 years, but only in terms of 15 to 20 years.

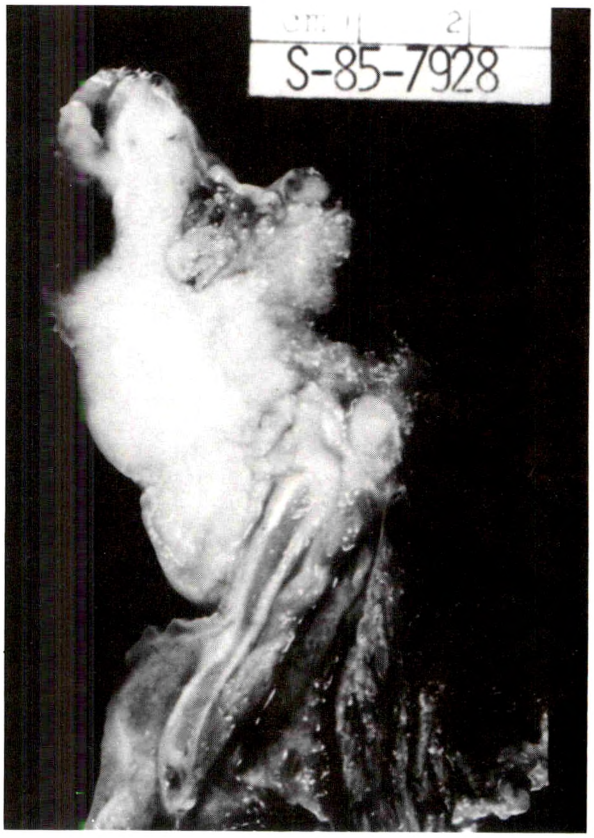

Fig 3. (Patient 6) Sagittal section of larynx demonstrating supraglottic adenoid cystic carcinoma with invasion of preepiglottic space.

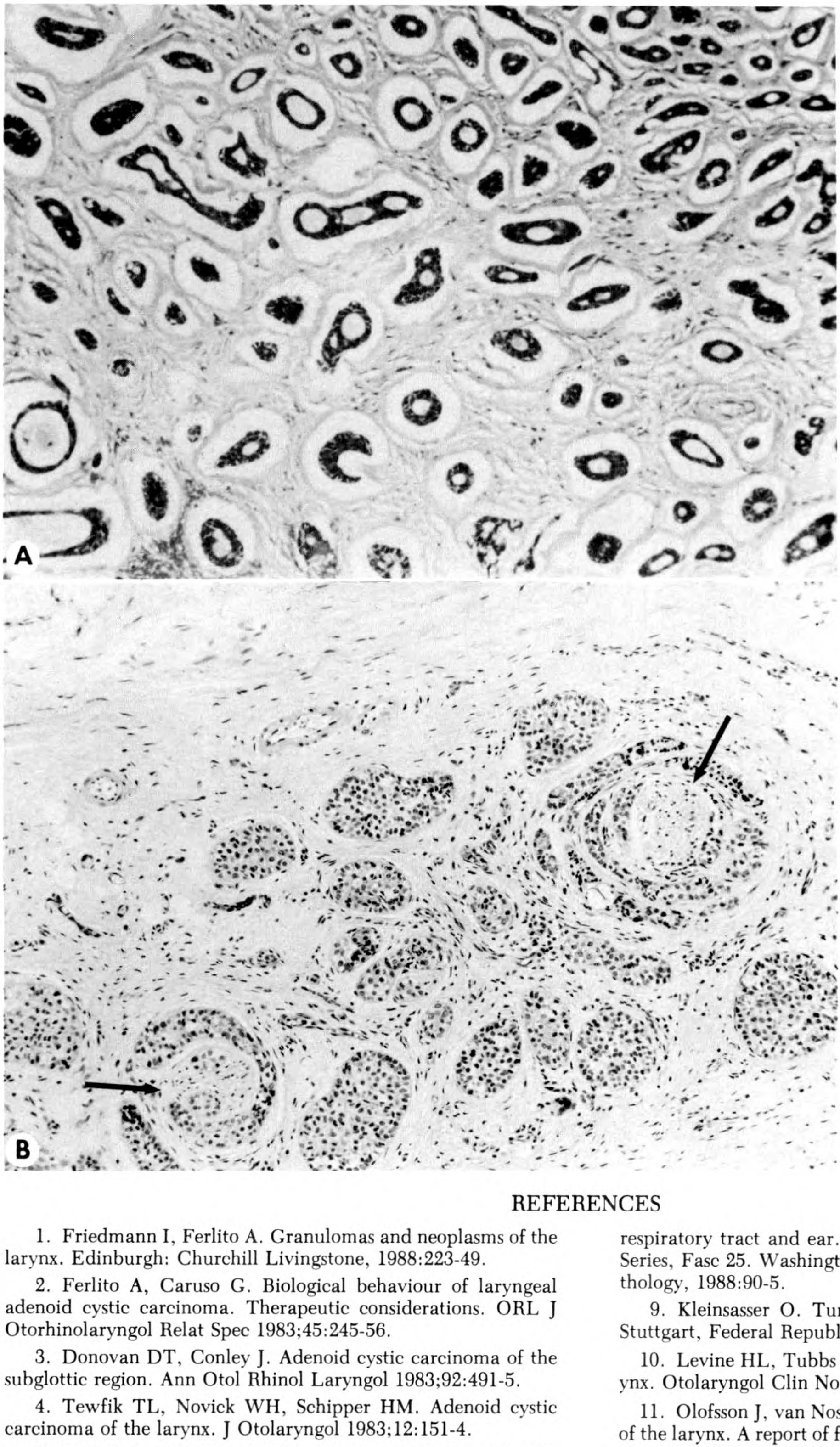

Fig 4. Adenoid cystic carcinoma. A) Tubular variant (H & E, medium stain and magnification). B) Solid variant, showing intraneural and perineural invasion (arrows) (H & E, light stain and low magnification).

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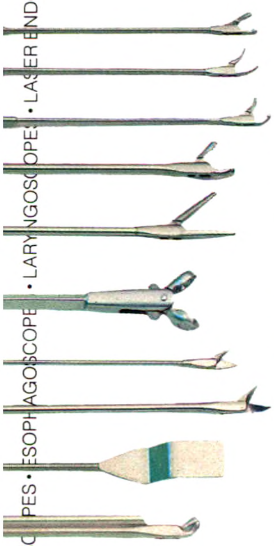

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VENTRAL CLEFT OF THE LARYNX: A RARE CONGENITAL LARYNGEAL DEFECT

SEYMOUR R. COHEN, MS, MD JEROME W. THOMPSON, MD

LOS ANGELES, CALIFORNIA

An anterior cleft of the larynx is apparently extremely rare. Only two patients with this defect have been reported in the American literature. The purpose of this paper is to present a child who was aphonic at birth and who was later found to have a congenital anterior cleft of the larynx. The diagnosis is established by the clinical symptoms, direct laryngoscopic examination, and radiographic studies. While severe voice change is the most prominent symptom of this defect, chronic aspiration is also a disquieting symptom, albeit controllable. The literature is reviewed, and the patient's symptoms and radiographic findings are documented. The clinical course over a period of almost 4 years is discussed.

KEY WORDS — cartilage larynx defect, chronic aspiration, cleft larynx, congenital anomaly of larynx, dysphonia.

INTRODUCTION AND LITERATURE REVIEW

Congenital anomalies of the larynx are of importance to the clinician because of their effects on laryngeal function. When any of the functions of the larynx are abnormal in a newborn or infant under 6 months of age (ie, voice change, loss of protection with aspiration, and/or respiratory obstruction), a congenital defect of the larynx should be suspected.

This paper presents a patient with an anterior cartilaginous laryngeal cleft, a rare anomaly. Only two live patients with this abnormality have been reported in the American literature. Because this congenital defect is compatible with life and its findings are not generally known, its recognition may be difficult or the defect may be unsuspected and remain undiagnosed. It is possible that the anomaly is more common than reported but has not been clinically recognized. Patients with posterior clefts of the larynx of varying severity have been diagnosed and reported with increasing frequency, although the defect was once thought to be rare.

A patient with an anterior cleft of the larynx is reported herein. One of the two patients reported in the American literature had severe voice change. This case was reported by Montgomery and Smith[1] before the American Laryngological Association in 1976. Discussion at the time of the presentation questioned the authors' diagnosis and brought up the possibility of a fracture of the larynx rather than a congenital defect. Two surgical procedures were necessary to correct the very high-pitched "female voice" in this male adolescent patient. At the 1988 meeting, Schild and Mafee[2] reported the second patient, one with cancer of the larynx, in whom a computed tomographic (CT) scan taken to evaluate the extent of the tumor revealed an anterior thyroid cartilage defect. This radiographic finding was confirmed by whole-organ section of the surgically removed larynx. Neither of these reports described the larynx as seen by endoscopic examination.

Cartilaginous defects of the larynx have been reported by Semon,[3] and it was Hutter[4] who described the postmortem finding of an infant with a wide anterior nonunion of the thyroid cartilages.

EMBRYOLOGY

This defect arises from a disturbance in the development of the larynx. Better understanding of this developmental abnormality is based in its embryology.[5,6]

While the arytenoids and cricoid cartilages develop in the fifth-arch masses, the cricoid appears first as two laterally placed clusters, and the thyroid cartilage is primarily a fourth-arch derivative. If it has a fifth-arch element, this is a later addition.

The cricoid cartilage chondrifies bilaterally from a single center in the ventral arch of a precartilaginous template that encircles the infraglottic cavity. When these areas meet, they form the dorsal lamina. Each arytenoid chondrifies from a single center, and each half of the thyroid cartilage chondrifies from two such centers. In the stage 17 embryo, the wedge-shaped condensation of the mesodermal laryngeal anlagen becomes more clearly defined around the epithelial lamina, but the fields for the laryngeal cartilages and muscles are not clearly defined. At stage 19 or slightly earlier, the precartilage cells in the laryngeal region begin to take the shape of the future cartilages. The place in which cartilage is first seen or recognizable can be re-

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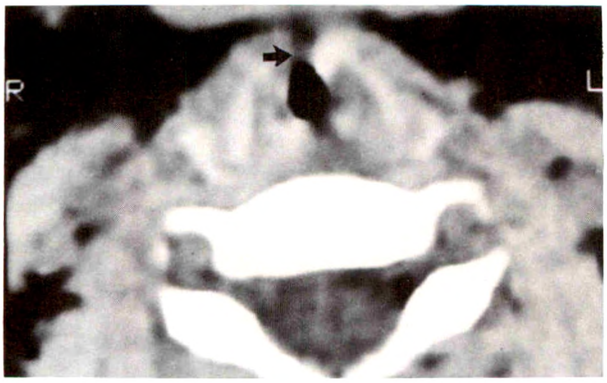

Fig 1. Computed tomographic scan of larynx, showing cartilage defect (arrow) in anterior commissure area. Dome-shaped configuration of larynx is shown.

garded as the chondrification center. It is at this stage (19) that four chondrification centers are present.

At stage 21, the pharyngeal mesoderm gives rise to the laryngeal cartilages and intrinsic musculature. The caudal part and the dorsal chondrification have fused with the muscles of the dorsal border of the chondrifying lamina, leaving a gap above the union. The ventral borders of the lamina begin to meet during the 9th week, and fusion is complete by the 12th week of embryogenesis. Individual muscles are recognized by stage 23.[5]

The muscles of the larynx depend for their differentiation on the development and growth of the cartilage. The intrinsic muscles are derived from two planes of circularly arranged cells; the inner plane belongs to the fifth arch and gives origin to the internal muscles that depend for their differentiation on the growth of the cartilages, while the outer plane belongs to the fourth arch and appears to give rise to the cricothyroid as a part cut off from the remainder (inferior constrictors) by the downgrowth of the lower thyroid cornu.[5,6]

Since the embryologic development of these muscles is so dependent on cartilaginous framework development, it is probable that in the larynx with an anterior cleft there may be defective muscle development — something not as yet determined. To summarize, as early as stage 15 in the 5- to 8-mm embryo, mesenchymal condensation is seen in the transverse section as an isosceles triangle, the apex of which is directed ventrally. This is the anlage of both the cartilages and the intrinsic muscles. From the shape and site of the wedge-shaped areas, it is presumed that the ventrolateral margins are the anlagen of the thyroid cartilage, while the caudal arch is the anlage of the cricoid. The thyroid cartilage originates in the first month in the fourth arches as lateral condensations of cells. By the end of the sixth week, chondrification has progressed considerably.

In the evolution of the larynx, Negus[7] reports that the earliest form of the larynx, such as is seen in the mudfish, is to protect the lungs from intrusion of water by a sphincter. There is no evidence of cartilage in this early form, and the larynx is only a muscular organ. Later, in the lungfish, a cartilage plate is developed to allow muscular attachment for better pull on the margins of the glottis.

The next stage of development is the laying down of cell condensation for the formation of secondary cartilages in the shape of an incomplete ring. This is fused to form the cricoid, but also represents the thyroid cartilage of higher species. When one compares the larynx with an anterior cleft with the larynx of earlier forms of animal life, it appears similar to the larynx of a lace monitor lizard. The valvular aperture is seen as a Gothic arch on coronal sections in this early form of animal. This is very similar to the laryngeal findings of the patient herein reported.

CASE REPORT

The patient is a female born Oct 5, 1984, who was first seen at 13 days of age. The chief complaint was a very weak and husky voice. The infant was the product of a full-term vaginal delivery with a birth weight of 30 kg and was noted to have excessive mucus in the airway that required repeated suctioning. There was no airway obstruction, but her cry was aphonic. Laryngoscopy performed elsewhere revealed laryngeal paralysis, and she was referred for evaluation of the laryngeal problem.

A preoperative examination showed a normal infant with severe dysphonia. On Oct 19, 1984, direct laryngoscopy revealed the following findings. The true vocal cords were somewhat thickened and webbed anteriorly, with the appearance of a Cohen type 1 web.[8] Considerable secretions were present, a culture of which showed no pathogens. There was also a minimal subglottic swelling in the anterior commissure.

The child was seen again on April 24, 1985, at approximately 6 months of age. Her chief complaints were severe dysphonia and a tendency to choke on liquids. Direct laryngoscopy showed findings similar to those seen at the first laryngoscopy, but the subglottic swelling was no longer present. It was assumed that the previously noted subglottic reaction was due to the trauma of the suctioning that was required at birth. In January 1988 she was treated for aspiration pneumonia.

She was referred by her speech pathologist on Feb 3, 1988, at the age of 3 years 4 months. In the interim, the child had been found to have a patent ductus arteriosus that was then surgically corrected. On this admission, a direct laryngoscopy showed a grossly abnormal larynx. The anterior commissure was wider than normal, appearing as a web. The normal triangular apex usually seen in this area was

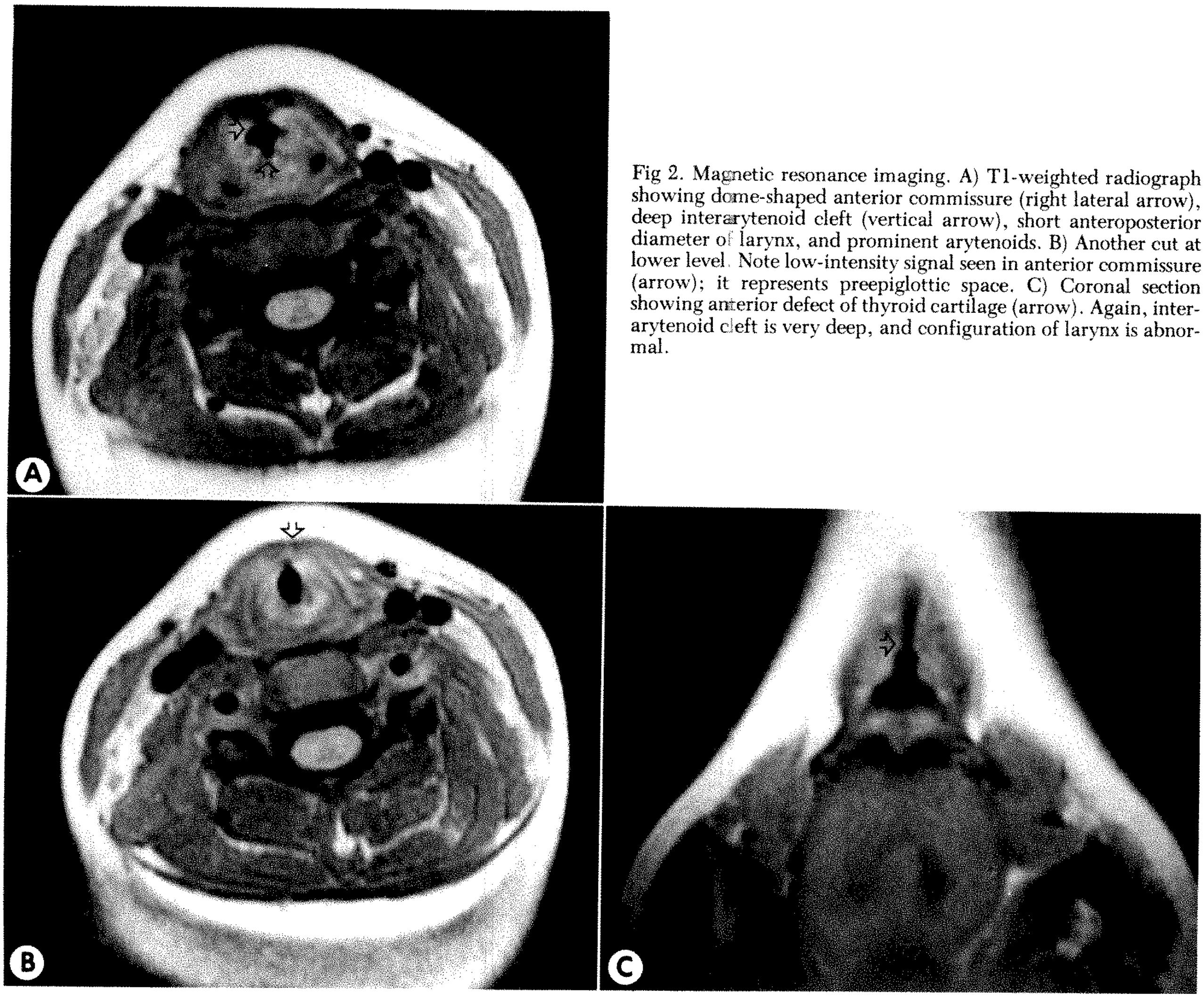

Fig 2. Magnetic resonance imaging. A) T1-weighted radiograph showing dome-shaped anterior commissure (right lateral arrow), deep interarytenoid cleft (vertical arrow), short anteroposterior diameter of larynx, and prominent arytenoids. B) Another cut at lower level. Note low-intensity signal seen in anterior commissure (arrow); it represents preepiglottic space. C) Coronal section showing anterior defect of thyroid cartilage (arrow). Again, interarytenoid cleft is very deep, and configuration of larynx is abnormal.

obliterated. The subglottic region was normal. The anterior portion of the larynx appeared as a Gothic dome. The interarytenoid cleft was very deep, and the vocal processes appeared anteriorly placed. The true vocal cords appeared of normal texture, but were rounded and open posteriorly on adduction. The larynx failed to close completely. Abduction was within normal limits, as was the sensation of the larynx. The appearance of the larynx suggested an anterior cleft. A CT scan of the larynx (Fig 1) showed the abnormality of the anterior portion of the larynx. Magnetic resonance imaging of the larynx was performed with T1-weighted axial, sagittal, and coronal sectioning (Fig 2). The study could not be completed, because the child emerged from sedation. The findings were listed as follows:

1. The anteroposterior diameter of the larynx is rather small.
2. The arytenoids appear disproportionately large.
3. There is a prominent interarytenoid cleft.
4. The large arytenoids cause undue prominence of the posterior margins of the aryepiglottic folds.
5. The cricoid cartilage is clearly visible, and its major portion appears to be intact.
6. There may be some deficiency at the top of the right side of the cricoid.
7. The thyroid cartilages cannot be clearly seen, because the signal level is isointense with adjacent tissues.

There was, however, some rather low-signal material in the midline that bulged into the lower third of the preepiglottic space (Fig 2). This region would normally be a very bright signal. The exact nature of the low-signal region is not clear. The area in which one would normally see the thyroepiglottic ligament was occupied by air. This finding would be consistent with a clinical impression of a midline anterior cleft. There also appeared to be a midline defect in the region of the first tracheal ring: approximately 1 to 2 mm of soft tissue bulged into the airway at this level. The findings were somewhat unusual and were indistinct because of the level of the signal. There appeared to be a cleft anteriorly, and it involved the first tracheal ring, the upper part of the thyroid cartilage, and the thyroepiglottic ligament.

On July 25, 1988, the child again underwent

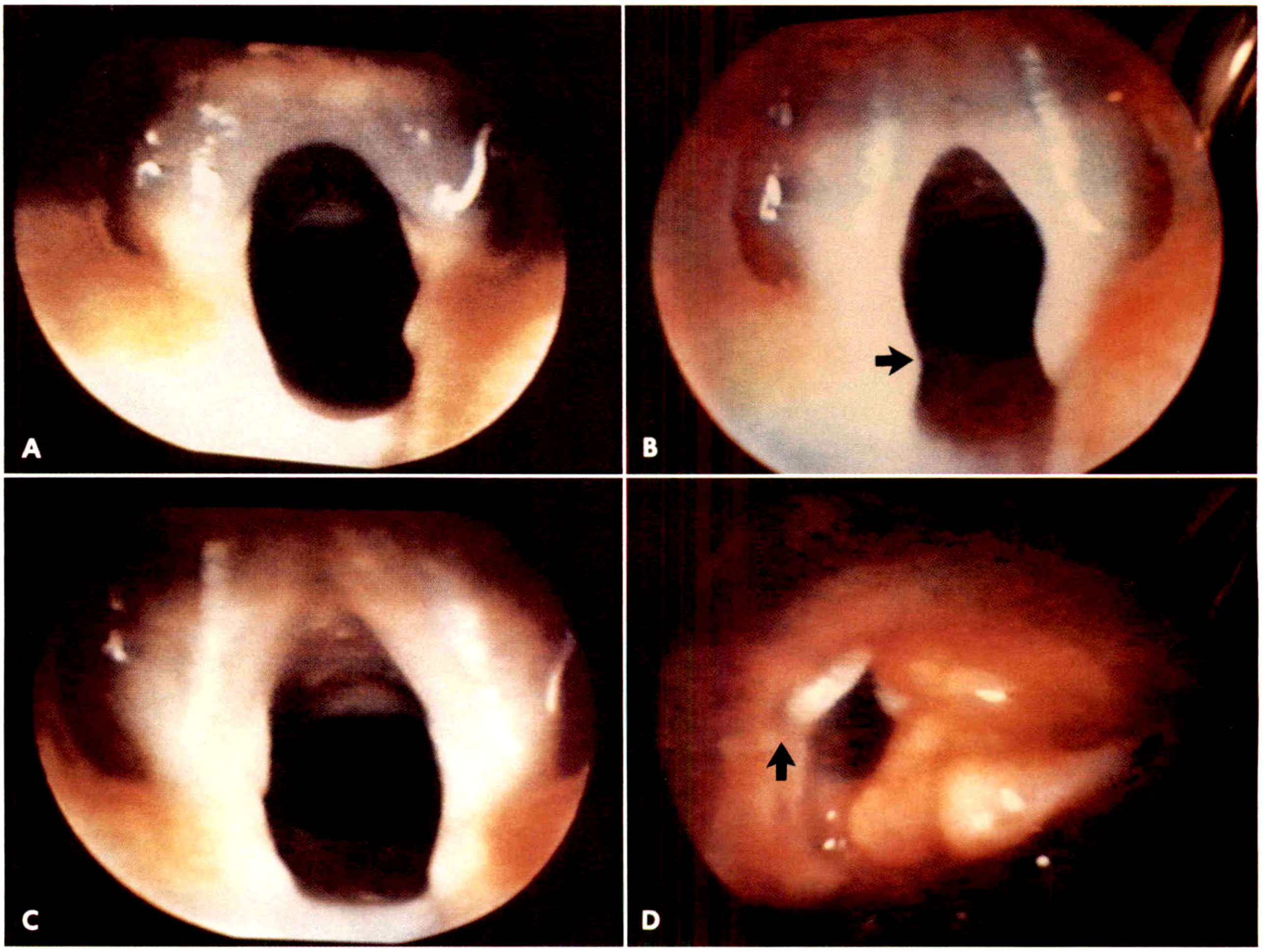

Fig 3. Endoscopic views of larynx. A) Rounded anterior commissure (arrow) suggests type 1 glottic web. B) Keyhole-type glottic opening (arrow), deep interarytenoid cleft, and dome-shaped anterior commissure. C) Anterior commissure has been separated, and subglottic area is seen anteriorly, showing intact tracheal rings. D) Deep interarytenoid cleft, prominent arytenoids, anterior position of vocal processes (arrow), and dome shape of anterior commissure.

laryngoscopy. Solid foods were taken readily, and she no longer aspirated liquids when they were taken slowly. The findings on direct laryngoscopy again showed webbing or rounding of the anterior commissure, normal abduction, a posterior glottic defect during adduction, elongated and diamond-shaped true vocal cords, a posterior-closure glottic defect, a deep interarytenoid cleft, prominent arytenoids, and a normal cricoid and upper trachea (Fig 3). A Patterson forceps was then placed into the larynx, and it could be palpated externally just under the skin, thus confirming the clinical impression of an anterior cleft of the larynx.

SUMMARY AND CONCLUSIONS

This paper presents historical data, embryology, comparative anatomy, and a review of the literature of the anterior cleft of the larynx. It also documents the findings and problems of a patient with this anomaly. The patient, first seen in early infancy, has been followed for approximately $3^{3}/_{4}$ years. The symptoms and difficulties in diagnosis are reported. It is probable that this lesion, which produces severe dysphonia in most patients and aspiration in some patients, may be more common than has been reported previously in the literature. When direct laryngoscopy in a patient with dysphonia (with or without aspiration) reveals the following findings, an anterior cleft of the larynx should be suspected:

1. A larynx with a small anteroposterior diameter.
2. Large arytenoids.
3. A prominent interarytenoid cleft.
4. A Gothic dome–like appearance of the anterior commissure.

It is apparent from this report that the diagnosis is much easier than the therapy or management. The child in this report was continued on voice retraining by a speech therapist, and has improved to the point that the parents no longer would consider surgical therapy.

In this cost-conscious period of medicine it may be unnecessary to use radiographic studies, such as a CT scan or magnetic resonance imaging, when the simple use of a Patterson forceps inserted into the anterior commissure during endoscopy will suffice to establish this diagnosis.

The therapy of this defect, at least as seen to be adequate in this patient, is to thicken the feedings very early and to give liquids very slowly. Speech therapy was effective. In some patients with very severe voice change and/or aspiration, laryngofissure and closure of the cleft or some type of phonosurgery may be necessary.

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HUMAN LEUKOCYTE ANTIGENS -A, -B, -C, AND -DR AND NASOPHARYNGEAL CARCINOMA IN NORTHERN CHINA

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We observed HLA associations in patients with nasopharyngeal carcinoma from northern China. There was an increased risk of nasopharyngeal carcinoma associated with HLA-B35 and a difference in the HLA association between patients with early- and late-onset disease. The frequency of B35 was significantly higher in patients than in control subjects, especially in early-onset patients (less than 30 years old). Late-onset patients had a higher frequency of DR2 as compared with normal subjects.

KEY WORDS — HLA, nasopharyngeal carcinoma.

INTRODUCTION

The association between nasopharyngeal carcinoma (NPC) and HLA-A2, -Bw46, and -B17 has been determined among Chinese patients from Singapore, Malaysia, Hong Kong, and Guangdong Province of the People's Republic of China. The incidence of NPC was known to be higher among the Chinese in Guangdong Province (southern China) than among those in northern China. The aim of our study is to determine whether the association between NPC and specific HLAs can be found in patients from northern China as well.

MATERIALS AND METHODS

Lymphocytes were separated with a Ficoll-Conray density gradient, and T and B cells were separated with nylon fiber columns. Typing of HLA was carried out with the microlymphocytotoxicity test (NIH method).[1] In the test, lymphocytes (antigens) combine to specific HLA antibodies in antisera and die following the addition of complement. Following cell death, the dead cells represent the HLA type of the test subject and can be identified. Antisera used were supplied by the Third Asia-Oceania Histocompatibility Workshop Conference.

A total of 24 unrelated Hans from northern China with NPC and 50 normal Hans as controls were studied. The patients were also divided into early-onset (less than 30 years old) and late-onset (more than 30 years old) groups.

TABLE 1. ANTIGEN FREQUENCIES OF SOME HLA-As AND -Bs IN PATIENTS AND CONTROL SUBJECTS

Antigen	*Patients With NPC (n = 24)*	*Control Subjects (n = 50)*	χ^2	*Fisher's p*	*RR*
A2	70.8%	52.0%	2.36	.063	2.24
Bw46	8.3%	6.0%	0.14	.086	1.42
B17	12.5%	16.0%	0.09	.260	0.75
B35	37.5%	14.0%	5.28	.019	3.69

NPC — nasopharyngeal carcinoma.

The calculation of the antigen frequency and gene frequency was based on the results of HLA typing. The significance of the difference in antigen frequency between patients and control subjects was calculated by Fisher's exact p value, and this value was multiplied by the number of antigens typed for to get the corrected p value (pc). The relative risk (RR) was calculated by the odds ratio in the classic 2 x 2 table. If a, b, c, and d represent the number of patients with an HLA antigen, of patients without this antigen, of control subjects with this antigen, and of control subjects without this antigen, respectively, the RR can be obtained from a x d divided by b x c. An RR > 1 means a high risk of getting a disease.

RESULTS

Some of the HLA-A and -B antigen frequencies in patients and control subjects are shown in Table 1. Compared to control subjects, patients had a higher frequency of B35. Hence, there was an increased risk of NPC associated with this antigen ($\chi^2 = 5.28$, Fisher's p = .019, RR = 3.69). But this difference

TABLE 2. DISTRIBUTION OF HLA-DR ANTIGENS IN PATIENTS AND CONTROL SUBJECTS

	Patients (n = 24)		*Control Subjects (n = 50)*	
HLA-DR	*FI*	*GI*	*FI*	*GI*
1	0.0417	0.0211	0.0800	0.0408
2	0.5000	0.2929	0.3400	0.1876
3	0.0833	0.0426	0.1600	0.0835
4	0.1667	0.0871	0.3000	0.1633
5	0.3333	0.1835	0.2800	0.1515
W6	0.0417	0.0211	0.0800	0.0408
7	0.2500	0.1340	0.2917	0.1584
W8	0.1250	0.0646	0.0800	0.0408
W9	0.2083	0.1102	0.3800	0.2126
Single blank	0.2500	0.1340	0.2917	0.1584

FI — antigen frequency, GI — gene frequency.

From the Beijing Institute of Otorhinolaryngology (Zhu, Liu), the Capital Institute of Medicine (Chen), and the Bei Tai Ping Lu Hospital (Kong), Beijing, People's Republic of China.

TABLE 3. HLA ANTIGEN FREQUENCIES IN NASOPHARYNGEAL CARCINOMA PATIENT SUBGROUPS AND CONTROL SUBJECTS

	B35			*DR2*		
	Early-Onset Patients *(n = 5)*	*Total Patients* *(n = 24)*	*Control Subjects* *(n = 50)*	*Late-Onset Patients* *(n = 19)*	*Total Patients* *(n = 24)*	*Control Subjects* *(n = 50)*
Frequency	60%	37.5%	14%	63.2%	50%	34%
χ^2	6.47	5.28	—	4.80	1.74	—
Fisher's p	.034	.019	—	.021	.085	—
RR	9.21	3.69	—	3.32	1.94	—

was not significant when p was corrected (pc>.05). The frequency of A2 was higher in NPC groups than in control subjects (70.8% versus 52.0%), but this difference was not statistically significant.

The HLA-DR antigen frequencies of the patients and control subjects are shown in Table 2. Compared to control subjects, patients had a higher frequency of DR2 (50% versus 34%) and a lower frequency of DR4 (16.7% versus 30%). Although no statistical significance was found, this is the first report about HLA-DR antigen distribution among NPC patients in northern China, and these data may be useful in future studies.

There was no association between HLA-C and NPC in these patients.

The association between HLA and the onset age of NPC is shown in Table 3. In our study, early-onset patients have a higher frequency of B35 ($\chi^2 = 6.47$, RR = 9.21, Fisher's p = .034) as compared with control subjects. Late-onset patients have a higher frequency of DR2 ($\chi^2 = 4.80$, RR = 3.32, Fisher's p = .02) than control subjects. However, neither of the differences was significant when corrected.

DISCUSSION

In the past, researchers pointed out that such antigens as A2, B17, B18, Bw46, and DR-double-blank brought a high risk of NPC, while A11 and DR4 were "safe" antigens.[2-6] In our study, the frequency of A2 was higher in patients than in control subjects, but the difference was not statistically significant. Among northern Chinese patients, we have not found any higher frequency of Bw46 or B17, which were reported by Ou et al[3] previously as dangerous factors for patients in southern China. In that study, higher frequencies of Bw46 and B17 were found among patients from the Guangzhou region in southern China, where NPC has a high incidence. In 1982, Cui and Lin[2] studied the association between HLA-A and -B antigens and NPC among patients from northern China. The frequency of B17 was higher in patients than in control subjects, but the difference was not statistically significant when the p value was corrected. The results of our study indicated that there was an increased risk of NPC associated with B35 in patients from northern China.

A previous study in southeastern Asia also showed that there was a different HLA association between early- and late-onset patients.[4] Bw46 was associated only with late-onset patients, whereas B17 was associated with all patients and particularly with early-onset patients. In our study, the early-onset group had a higher frequency of B35. Late-onset patients had a high frequency of DR2.

In summary, we suggest that in northern China, NPC patients have a particular HLA antigen association that is different from that of southern Chinese patients, as well as patients outside of China. This difference may be due to geographic and genetic factors. This discovery may be of benefit to NPC patients in northern China in the aspects of forecast, prevention, early diagnosis, and treatment.

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VARIABILITY OF THE SURGICAL ANATOMY OF THE NEUROVASCULAR COMPLEX OF THE CEREBELLOPONTINE ANGLE

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The variability of the anatomic relationship of the anterior inferior cerebellar artery (AICA) to the facial (seventh) and vestibulocochlear (eighth) nerves was studied in 52 cerebellopontine angles (CPAs) from 26 adult cadavers. The AICA originated from the basilar artery (98.1%) or from the vertebral artery (1.9%) as a single (92.3% of CPAs) or duplicate (7.7%) artery. Each of the 52 CPAs had one or more arterial trunks that coursed in close proximity to the seventh and eighth cranial nerves and thus were said to be nerve-related. The nerve-related arterial trunks were divided into three segments based on their relationship to the nerves and meatus: the premeatal, meatal, and postmeatal segments. The nerve-related branches of the AICA gave rise to the internal auditory artery in 92.3% of the CPAs, the recurrent perforating artery in 78.8%, and the subarcuate artery in 30.8%. The importance of understanding the surgical anatomy of the neurovascular complex of the CPA when performing a vestibular neurectomy is reviewed.

KEY WORDS — anterior inferior cerebellar artery, basilar artery, cerebellopontine angle, facial nerve, neurovascular complex, vestibulocochlear nerve.

INTRODUCTION

Total or partial section of the eighth cranial nerve as a treatment for intractable vertigo has been performed and reported by many neurotologists. Several methods of approaching the cerebellopontine angle (CPA) have been developed: occipital,[1-3] middle cranial fossa,[4-7] translabyrinthine,[8-10] retrolabyrinthine,[7,11] and retrosigmoid approaches.[12] With these advances in vestibular neurectomy, the anatomy of the CPA has also been studied in categories such as the shape and course of the anterior inferior cerebellar artery (AICA),[13,14] the origin of the internal auditory artery (IAA),[15-22] the histologic features of the seventh and eighth cranial nerves,[23-27] and the branches of the AICA by means of angiography.[21,28]

Thus, a more profound and precise understanding is required of the anatomic relationships between the cranial nerves and the AICA with its tributaries at the CPA, especially around the internal auditory canal.

The purpose of this investigation is to describe the variability of anatomic relationships between the trunks and branches of the AICA and the seventh and eighth cranial nerves.

MATERIALS AND METHODS

Fifty-two CPAs from 26 cadavers of adults ranging in age from 21 to 84 years with a median age of 62 provided the material for this study. Fifteen male and 11 female cadavers were included. The calvarium was removed, and the occipital bone was wedge-resected. The cerebellar tentorium was sectioned, and the cerebellum was retracted to provide a posterior view of the CPA. The AICA and the seventh and eighth cranial nerves were then examined with the operating microscope (Fig 1).

After this examination from the rear, the dura was opened, and the posterior wall of the internal auditory canal was removed with a drill to provide a suboccipital-transmeatal view of the CPA (Fig 2). The cerebrum and cerebellum, with nerves and arteries intact, were then removed from the skull for reexamination of the origin, course, and termination of the vessels related to the seventh and eighth cranial nerves (Fig 3).

To determine the spatial location of the nerves and the vessels in the CPAs, the AICA was divided into three segments (Fig 4A), and the nerve-related vessels were localized to one of nine imaginary three-dimensional partitions of the CPA (Fig 4B).

RESULTS

Anterior Inferior Cerebellar Artery. The AICA originated from the basilar artery (98.1%) or from the vertebral artery (1.9%) as a single vessel in 92.3% of the CPAs, but in four specimens (7.7%) it arose as two arteries (Table 1 and Fig 5).

The patterns of the AICA from its origin to the insertion were observed in 49 specimens: 16 AICAs coursed as a single artery in its whole length, and 29 AICAs arose as a single artery and divided into two major trunks before (28 AICAs) or after (1 AICA) passing near the seventh and eighth cranial nerves.

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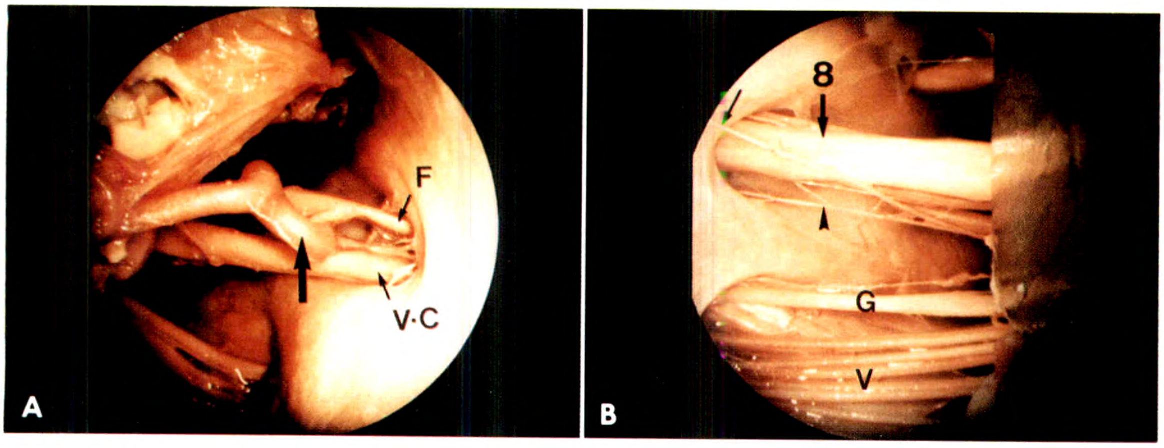

Fig 1. Microscopic views of CP angle. A) Right. F — facial nerve, V·C — vestibulocochlear nerve, arrow — AICA loop. B) Left. 8 — eighth cranial nerve, arrow — subarcuate artery, arrowhead — internal auditory artery, G — glossopharyngeal nerve, V — vagus nerve.

However, four AICAs coursed as duplicate arteries throughout their whole length.

The nerve-related trunks of the AICA were divided into three segments based on their relationship to the nerves and the meatus: the premeatal, meatal, and postmeatal segments (Fig 4A). Each of the three segments was composed of one or two arterial trunks — most commonly, one. The single nerve-related segments were formed from either a main or a rostral trunk that arose, in descending order of frequency, from a solitary AICA, a rostral duplicate AICA, or a caudal duplicate AICA.

The premeatal segment began at the basilar or vertebral artery and coursed around the brain stem to reach the seventh and eighth cranial nerves and the porus of the internal auditory meatus. The premeatal segment was composed of one or two arterial trunks. In the 52 CPAs, there were 56 nerve-related premeatal segments. Fifty (89.3%) of the 56 premeatal segments were anteroinferior to the nerves. The remainder were anterior, anterosuperior, posteroinferior, or inferior to the nerves (Table 2).

The meatal segment was located in the vicinity of the internal auditory meatus, where the nerve-related vessels turned toward the brain stem. This segment usually formed a laterally convex loop, the meatal loop, directed toward or through the meatus. The meatal segment was located medial to the porus in 52% of the 50 CPAs and reached the porus or protruded into the canal in 48% (Table 3). The loop of the AICA in this region was located most commonly between the nerves (44%) (Table 3). In the 52 CPAs, there were 69 nerve-related meatal segments, because a premeatal segment in 13 CPAs bifurcated near the nerves to yield two nerve-related meatal segments (Table 2). These segments were located between the nerves (44.9%), or inferior (33.4%) or posterior (21.7%) to the nerves. The meatal segment of the AICA passed above the eighth cranial nerve in 22.4% of the cases, between the seventh and eighth cranial nerves in 50%, and below the seventh cranial nerve in 27.6% (Table 1 and Fig 6A-C).

The postmeatal segment began distal to the nerves and coursed medially to supply the brain stem and the cerebellum. The 69 meatal segments found in the 52 CPAs gave rise to 65 postmeatal segments. There were four fewer postmeatal segments than meatal segments because two meatal segments anastomosed to form one postmeatal segment, and three meatal segments ended in the cerebellum near the meatus. The postmeatal segments were most commonly posteroinferior (36.9%) to the nerves; none were between the nerves (Table 2).

In summary, the most common course of the AICA in this study was anteroinferior to the nerves (premeatal), between the nerves (meatal), and posteroinferior to the nerves (postmeatal) (Fig 6D).

Internal Auditory Artery. The IAA branched off from the AICA and was identified in 48 of the 52 specimens (92.3%). We deduced that the IAAs of the remainder were destroyed during dissection. The IAA may occur as a single artery or as multiple

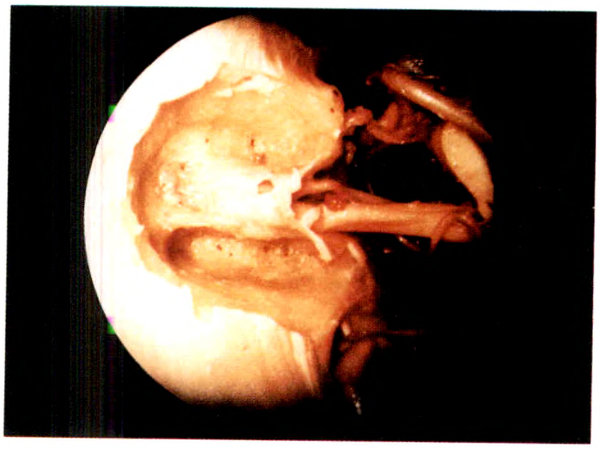

Fig 2. Drilling of petrous apex, showing drilled-out posterior meatal lip with intact dura covering seventh and eighth nerves.

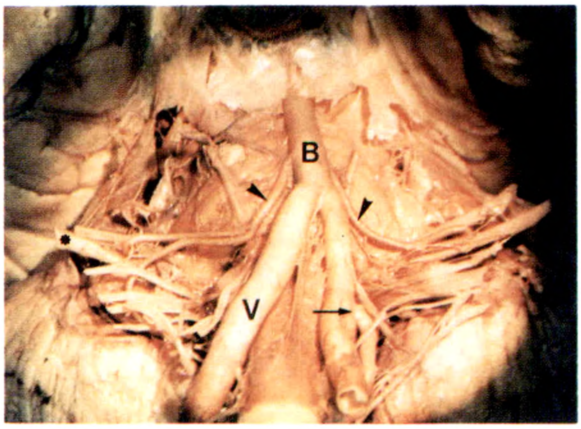

Fig 3. Inferior aspect of vertebrobasilar system. B — basilar artery, V — vertebral artery, arrowheads — AICAs, arrow — PICA, asterisk — eighth nerve.

arteries. The IAA was found to be a single artery in 27.1%, two arteries in 41.7%, three in 22.9%, and four in 8.3% (Table 4). One hundred of a total of 102 IAAs (98%) arose from the AICA, and the other two IAAs (2%) arose from the basilar artery (Fig 7). Of the 102 IAAs found in the 48 CPAs, 20 (19.6%) originated from the premeatal segment, 69 (67.7%) from the meatal segment, and 13 (12.7%) from the postmeatal segment. Sixty-eight (66.7%) IAAs passed between the seventh and eighth cranial nerves, 34 (33.3%) passed below the nerves, and none were above the eighth cranial nerve (Table 4). The IAAs passed most frequently posteroinferior to the nerves (38.2%) or between the nerves (29.4%). None were superior to the nerves (Table 5 and Fig 8).

Recurrent Perforating Artery. The recurrent perforating artery (RPA) was identified in 41 specimens (78.8%) of the 52 CPAs. There was one RPA in 48.8% of these 41 CPAs, two in 41.5%, three in 7.3%, and four in 2.4% (Table 4). Of the 67 RPAs observed in the 41 CPAs, 23 (34.3%) originated from the premeatal segment, 30 (44.8%) from the meatal segment, and 14 (20.9%) from the postmeatal segment. Forty-six RPAs (68.7%) passed above the eighth cranial nerve, 9 (13.4%) passed between the nerves, and 12 (17.9%) passed below the nerves (Table 4). The RPA was located most commonly posterosuperior (25.3%) or anterosuperior (19.4%) to the nerves (Table 5 and Fig 8).

Subarcuate Artery. The subarcuate artery (SA) was identified in 16 specimens (30.8%) of the 52 CPAs. There was one SA in 87.5% of the CPAs, and two in 12.5% (Table 4). Of the 18 SAs found in 16 CPAs, 10 (55.6%) originated from the premeatal segment, 1 (5.6%) from the meatal segment, and 7 (38.8%) from the postmeatal segment. Seventeen SAs (94.4%) passed above the eighth cranial nerve, and 1 (5.6%) below the nerves (Table 4). The SA was located most commonly anterosuperior (55.6%) to the nerves (Table 5 and Fig 8).

Posterior Inferior Cerebellar Artery. The posterior inferior cerebellar artery (PICA) was identified in 50 specimens (96.2%) of the 52 CPAs; two specimens (3.8%) had no PICAs. All 50 PICAs originated as a single vessel from the vertebral artery. They coursed most frequently inferior to the 9th, 10th, and 11th cranial nerves (58%). No branches of the PICA were identified supplying the inner ear.

Other Findings. At the porus acousticus, the seventh cranial nerve was in 27 cases located anteroinferior (54%) to the eighth cranial nerve, and in the remaining CPAs it was inferior in 18 (36%) and anterior in 5 (10%) (Fig 9).

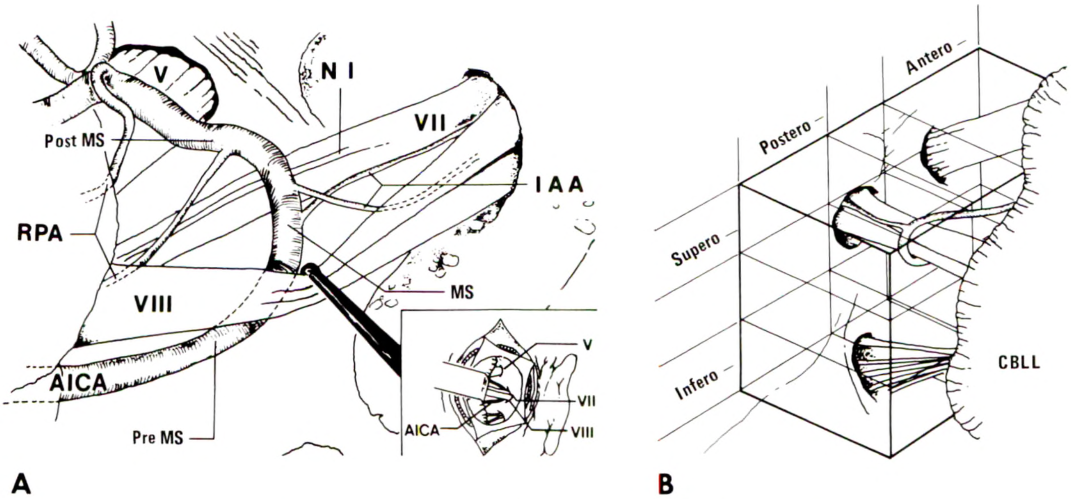

Fig 4. Determination of spatial location of nerves and vessels. A) Segments of AICA. Posterior view of right cerebellopontine angle. Trigeminal nerve (V) is anterior. Premeatal segment (PreMS) courses anterior to nerves. Vestibulocochlear nerve (VIII) is pulled backward to expose meatal segment (MS). Meatal segment passes between vestibulocochlear nerve posteriorly and nervus intermedius (NI) and facial nerve (VII) anteriorly. Internal auditory arteries (IAA) arise from meatal segment, and recurrent perforating arteries (RPA) arise from postmeatal segment (PostMS). Inset) Orientation. B) Location of nerve-related vessels. Posterior view of left cerebellopontine angle, which was divided into nine imaginary three-dimensional partitions in relation to nerves at meatus. CBLL — cerebellum.

TABLE 1. ORIGIN AND COURSE OF ANTERIOR INFERIOR CEREBELLAR ARTERY

	Single	*Duplicate*	*Total*
Origin			
Basilar artery	47	4	51
Vertebral artery	1	0	1
Total	48	4	52
Course			
Over eighth nerve	13	0	13
Between seventh and eighth nerves	26	3	29
Under seventh nerve	15	1	16
Total	54	4	58

The cleavage plane between the vestibular and cochlear nerves was discernible in 36 specimens (72%) of the 50 CPAs, and indiscernible in 14 CPAs (28%) (Fig 10).

The average length of the seventh and eighth cranial nerves from the origin to the porus acousticus was measured in 50 CPAs, and was found to be 11.32 mm (1 SD = 2.54). The average length from the porus to the lateral fundus was measured in 18 CPAs, where the posterior wall of the internal auditory meatus was drilled out, and was 8.93 mm (1 SD = 1.34).

DISCUSSION

The treatment for vertiginous patients varies according to the causes, and a definitive surgical procedure is required for patients whom conventional medical treatment has failed.

Historically, operations for the relief of vertigo have been performed by cutting the whole eighth cranial nerve, with resultant hearing loss.[29] Also, the facial nerve, which is accompanied by the eighth cranial nerve in the internal auditory canal, often becomes injured during the procedure, resulting in facial paralysis.

Vestibular neurectomy is never an easy procedure to perform, and thus a precise knowledge of the variable local anatomy of the CPA is required for a successful outcome.

Martin et al[14] reported the AICA as a single vessel in 72%, double in 26%, and triple in 2% of 50 CPAs. Naidich et al[21] reported the AICA to be single in 60%, double in 39%, and triple in 1% of their CPAs. In this study, the AICA originated as a single vessel in 92.3% and as a duplicate vessel only in 7.7%. There were no triple vessels found.

There have been various reports about the origin of the AICA, but in the majority, it originated from the basilar artery, and in some reports, it was from the vertebral artery, the PICA,[21] or even the cavernous portion of the internal carotid artery.[30]

Atkinson[13] reported that the AICA originated consistently from the basilar artery, and Rhoton[31] and Martin et al[14] reported the same result in all of their cases. In the present study, the majority (98.1%) of the AICAs originated from the basilar artery, and only one (1.9%) originated from the

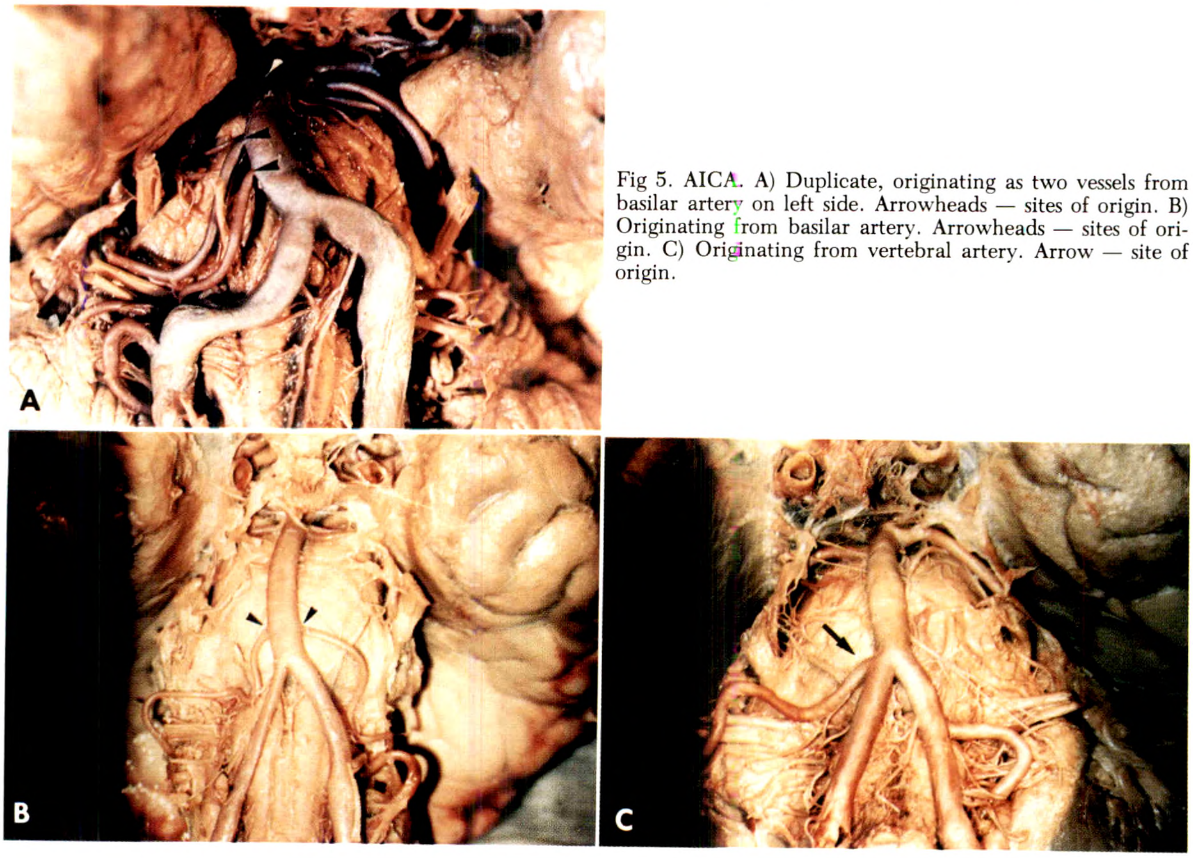

Fig 5. AICA. A) Duplicate, originating as two vessels from basilar artery on left side. Arrowheads — sites of origin. B) Originating from basilar artery. Arrowheads — sites of origin. C) Originating from vertebral artery. Arrow — site of origin.

TABLE 2. LOCATION OF NERVE-RELATED SEGMENTS OF ANTERIOR INFERIOR CEREBELLAR ARTERY

Location	*Premeatal*	*Meatal*	*Postmeatal*
Anteromeatal			
Anterosuperior	1		7
Anterior	1		4
Anteroinferior	50		6
Meatal			
Superior		15	11
Between		31	
Inferior	3	23	2
Posteromeatal			
Posterosuperior			10
Posterior			1
Posteroinferior	1		24
Total number	56	69	65

Thirteen premeatal segments were divided into two segments each, thus yielding total of 69 meatal segments. Two meatal segments anastomosed with each other, and three ended as meatal segment, thus yielding total of 65 postmeatal segments.

vertebral artery. Other investigations usually failed to observe the incidence in which the AICA originated from the vertebral artery.

In our study, the AICA most commonly originated as a single vessel and divided into rostral and caudal trunks before reaching the seventh and eighth cranial nerves, respectively, and finally ended in the cerebellum. This finding was in agreement with that of Martin et al.[14] The configuration of the AICA origin was symmetric in 37.5% of the specimens in our study, and symmetry in 43% of specimens has been reported.[16]

Sunderland[16] and Mazzoni[18] found the meatal segment at the porus or within the internal auditory canal in 64% and 67% of their CPAs, respectively. Mazzoni[18] found that the meatal segment was medial to the porus in 33%, reached the porus in 27%, and entered the canal in 40%, rarely reaching beyond the medial half of the canal. Sunderland[16] found it to be medial to the porus in 36%. Martin et al[14] reported that the meatal segment was medial to the porus in 46%, and at or within the canal in 54%. In our study, it was medial to the porus in 52% and at or within the canal in 48%. In our study, the meatal segments passed most frequently between the seventh and eighth cranial nerves, but Rhoton[31] reported that the meatal segment was usually inferior to the nerves. Our postmeatal segments were most commonly located posteroinferior to the nerves (36.9%), and none were between the nerves.

The IAAs were identified in 48 specimens (92.3%), and there was one IAA in 27.1% of the CPAs, two in 41.7%, three in 22.9%, and four in 8.3%. Our results are in agreement with those of Martin et al,[14] but differ from those of Sunderland[16] and Walker,[28] who reported that the IAA seldom had branches.

Mazzoni and Hansen[19] reported that the IAA was single in half of their CPAs and duplicate in the other half. In another study, Mazzoni[18] found three IAAs in 4% of the CPAs (Table 6[14,18]). In the present study, the IAA arose most frequently from the meatal segment of the AICA (67.7%). However, our results differed significantly from those of others. It was reported by others that the IAA arose from the premeatal segment in 64.7%[18] and 77%[14] of specimens. In our study, no cases of IAA originating from the RPA were observed; this finding differed from those of others. Martin et al[14] reported this origin in 23% of cases, and Mazzoni

TABLE 3. LOCATION OF ANTERIOR INFERIOR CEREBELLAR ARTERY LOOP

Location	*No.*	*%*
In relation to porus		
Medial to porus	26	52
At porus	17	34
Lateral to porus	7	14
Total	50	
In relation to nerves		
Anteromeatal		
Anterosuperior	0	0
Anterior	1	2
Anteroinferior	3	6
Meatal		
Superior	9	17
Between	23	44
Inferior	9	17
Posteromeatal		
Posterosuperior	6	12
Posterior	0	0
Posteroinferior	1	2
Total	52	

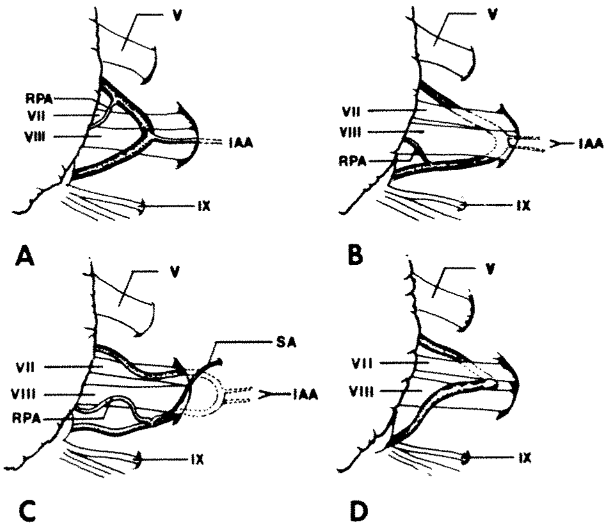

Fig 6. Location of AICA loop in relation to porus and nerves. V — trigeminal nerve, VII — facial nerve, VIII — vestibulocochlear nerve, IX — glossopharyngeal nerve. A) AICA courses superior to nerves, and loop is located medial to porus. IAA — internal auditory artery, RPA — recurrent perforating artery. B) AICA courses inferior to nerves, and loop is located at porus. C) AICA courses between nerves, and loop is located within porus. SA — subarcuate artery. D) Most common course of AICA in this study. AICA courses anteroinferior to nerves until it reaches porus, between nerves at porus, and posteroinferior thereafter.

TABLE 4. NUMBER, ORIGIN, AND COURSE OF NERVE-RELATED BRANCHES OF ANTERIOR INFERIOR CEREBELLAR ARTERY

	Branch (No.)		
	IAA	*RPA*	*SA*
No. of CPAs with branches	48	41	16
No. of branches per CPA			
1	13	20	14
2	20	17	2
3	11	3	
4	4	1	
Total number of branches	102	67	18
Arterial segment of origin			
Premeatal segment	20	23	10
Meatal segment	69	30	1
Postmeatal segment	13	14	7
Course of branches			
Over eighth nerve		46	17
Between seventh and eighth nerves	68	9	
Under seventh nerve	34	12	1

CPA — cerebellopontine angle, IAA — internal auditory artery, RPA — recurrent perforating artery, SA — subarcuate artery.

and Hansen[19] also mentioned that the IAA may arise from the RPA or SA. Ninety-eight percent of the IAAs identified in this study arose from the AICA, and the remainder arose from the basilar artery.

The IAA has been described as either a branch of the basilar artery that passes parallel to the AICA just above it,[32,33] or simply as a branch of the basilar artery.[34,35] It has been reported that the IAA arose from the AICA in 60% to 100% of cases (60% to 80%,[17] 80%,[19] 89%,[22] and 100%[14]). It has also been reported that the IAA arose from the basilar artery in 17% to 40% of cases.[15-17,28,36] Our data showed only one case in which the IAA originated from the basilar artery; the majority originated from the AICA. This variability could be due to a large extent to differences in the definitions of IAA and AICA used in various studies, and to a lesser extent to racial differences.

Mazzoni and Hansen[19] reported that 17% of the IAAs arose from the accessory AICA, and 3% from the PICA. Park and Chang[22] reported that 9% of the IAAs arose from the middle cerebellar artery, and the accessory AICA was the same vessel as the middle cerebellar artery that they described in their reports. The present study failed to observe the IAA branching off from the accessory AICA, PICA, or middle cerebellar artery. Walker[28] mentioned that in cases in which the IAA originated from the basilar artery, the AICA was much smaller in size than usual. The present data differed from those of Walker's report. We believe that this discrepancy is caused by differences in the definitions of the IAA and the AICA used in various studies.

In our study and that of Martin et al,[14] the trunk of origin on the basilar artery of an artery sending branches to the internal auditory canal was called the AICA if it sent branches, although small, to the cerebellum. The site of origin of the IAA was defined as the point at which the trunk of the AICA sends branches to the cerebellum. On the other hand, Nager[36] and Sunderland[16] called the trunk of origin on the basilar artery an IAA rather than an AICA if the branch entering the meatus was larger than the branch reaching the cerebellum.

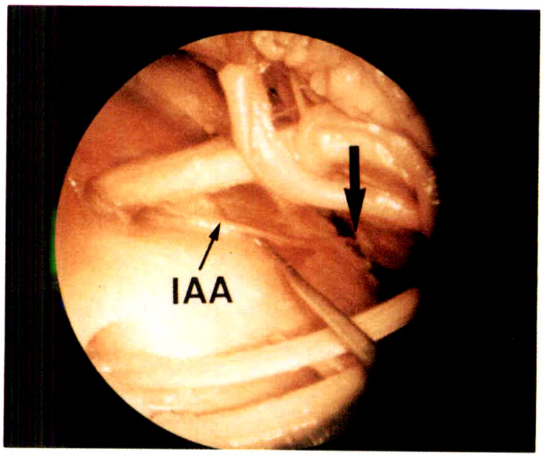

Fig 7. Internal auditory artery (IAA) originated from basilar artery. Arrow — site of origin.

Mazzoni[18] reported that the IAA arose from the PICA in a few cases (3%), as did Park and Chang (2%),[22] but we failed to observe such findings in our study. The IAA coursed most commonly between the seventh and eighth cranial nerves (66.7%). Fisch[20] reported that the artery passing between the facial and the acoustic nerves in the anterior half of the canal is the artery supplying the cochlea.

The RPA arose most commonly from the meatal segment (44.8%), but the results of Martin et al[14] showed that the RPA arose most commonly from the premeatal segment. The location of the RPA in relation to the nerves showed marked variation, so the RPAs were evenly distributed in the CPAs.

TABLE 5. LOCATION OF ORIGINS OF BRANCHES OF ANTERIOR INFERIOR CEREBELLAR ARTERY IN RELATION TO NERVES

Location	*IAA*	*RPA*	*SA*
Anteromeatal			
Anterosuperior	1	13	10
Anterior	5	6	
Anteroinferior	13	3	1
Meatal			
Superior		8	2
Between	30	5	
Inferior	10	5	
Posteromeatal			
Posterosuperior	1	17	3
Posterior	3	5	2
Posteroinferior	39	5	
Total number	102	67	18

IAA — internal auditory artery, RPA — recurrent perforating artery, SA — subarcuate artery.

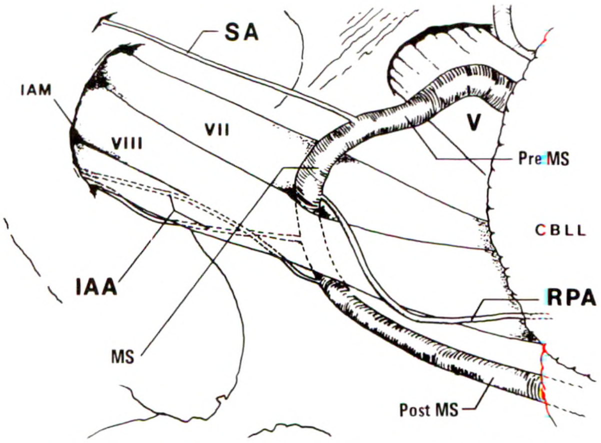

Fig 8. Courses of nerve-related vessels of AICA. This posterior view of left cerebellopontine angle illustrates most commonly observed cases in this study. Internal auditory artery (IAA) originates from meatal segment of AICA and is located posterosuperior to and passes between nerves. Recurrent perforating artery (RPA) originates from premeatal segment (PreMS) of AICA and is located posterosuperior to and passes above eighth nerve (VIII). Subarcuate artery (SA) originates from PreMS of AICA and is located anterosuperior to and passes above nerve VIII. V — fifth cranial nerve, VII — seventh cranial nerve, MS — meatal segment, PostMS — postmeatal segment, IAM — internal acoustic meatus, CBLL — cerebellum.

The SA arose most commonly from the premeatal segment (55%), but Martin et al[14] reported that the SA arose most commonly from the postmeatal segment (in 42%), and there was only one SA per CPA. The SA supplied the mastoid in the region of the semicircular canals. The subarcuate canal is recognized as a potential route for extension of infections from the mastoid region to the meninges and the superior petrosal sinus.[23,36] The AICA was adherent to the dura lining the subarcuate fossa at the site of origin of the SA in one (6.3%) CPA. There was a report that this adherence was found in 10% of the specimens.[19] Nager[36] noted that the SA is rarely mentioned in the description of the arteries in this area. This is probably because the artery and its connection to the bone are destroyed when the brain is retracted or removed from the skull. Nager[36] found that the most frequent site of origin of the SA was the IAA rather than the AICA, a difference explained by the discrepancy in definitions of the AICA and the IAA as mentioned previously. That the SAs were identified in only 30.8% of the CPAs in this study may be the result of artifacts.

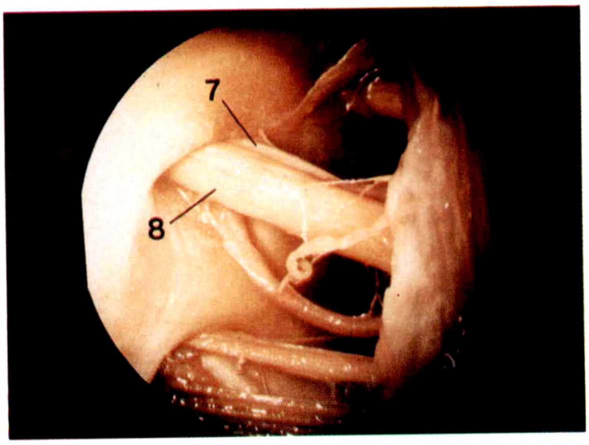

Fig 9. Location of seventh cranial nerve (7), which is anteroinferior to eighth nerve (8).

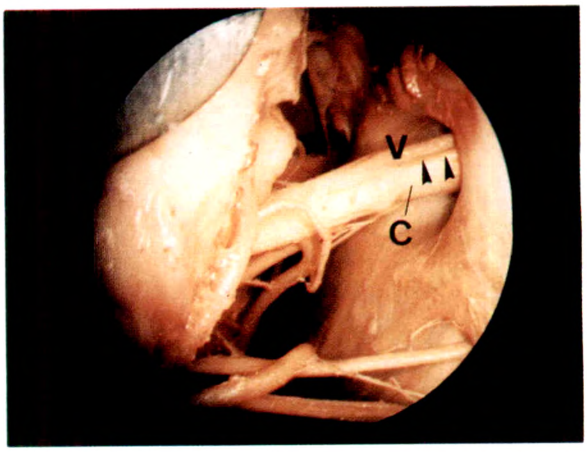

Fig 10. Cochlear-vestibular cleavage plane (arrowheads). C — cochlear nerve, V — vestibular nerve.

The PICA was identified in 50 specimens (96.2%) as a single vessel. The site of origin was the vertebral artery. The PICA passed most frequently below the 9th, 10th and 11th cranial nerves (58%). Lister et al[37] reported that the PICA existed in 84% of 50 CPAs, with one case of duplicate PICA, and the PICAs passed most frequently through the rootlets of the 11th nerve. The branches of the PICA supplying the inner ear were reported in 3% of specimens.[19] Park and Chang[22] reported a 2% incidence of those branches when the AICA was absent. In our study, no branches of the PICA were observed to supply the inner ear.

At the porus, the seventh cranial nerve was located anterior (10%), anteroinferior (54%), or inferior (36%) to the eighth cranial nerve. Chouard[38] reported that the superior vestibular, facial, and Wrisberg intermediate nerves are in the same pial sheath, so that great care should be taken during dissection. The intermediate nerve was reported to pass the CPA adhering to the eighth cranial nerve.[25] It is thought that increased parasympathetic tone is one of the causative factors of Meniere's disease.[38,39] The intermediate nerve is related to the autonomic nervous system of the inner ear, so it is desirable to section the intermediate nerve together with the vestibular nerve when performing vestibular neurectomy.[38]

TABLE 6. NUMBER OF INTERNAL AUDITORY ARTERIES

No.	*Mazzoni*[18]	*Martin et al*[14]	*This Study*
1	51%	30%	27.1%
2	45%	54%	41.7%
3	4%	14%	22.9%
4	0%	2%	8.3%

During the surgical procedures with various approaches, transient facial paralysis persisting from the second to the seventh postoperative day through several weeks was reported in 3.6%,[40] 4%,[41] 5%,[42] and 7%[20] of cases. Complete facial paralysis was reported in 17.5%.[43] Hearing loss was reported in 7.2%,[40] 9%,[44] and 31%.[45] Thus, discrimination of the vestibular nerve from the facial and cochlear nerves cannot be overemphasized. Rhoton[46] reported that the cochlear nerve was located 1 mm anterior to the facial nerve in his 200 cadaver dissections. House et al[47] reported that the portion in which the vestibular and cochlear divisions separate was somewhat narrower than other portions of the eighth cranial nerve. This has been referred to as having an hourglass appearance.[12,45] The vestibular division is more grayish in color because of the difference in the amount of myelin,[47] and it is larger than the cochlear division in about 80% of cases.[24] We confirmed these findings in our study.

Schefter and Harner[27] reported that discrimination between the vestibular and cochlear nerves is usually difficult with the suboccipital approach. However, Silverstein and Norrell[48] reported that the cleavage plane usually disappears at 3 to 5 mm from the root entry zone, so that it is possible to discriminate the plane in about 70% of specimens. Silverstein et al[12,26] reported that the cleavage plane was discernible in 73% to 75% of cases with the retrolabyrinthine approach. In the present study, the cleavage plane between the vestibular and cochlear nerves was discernible in 72% of the specimens without drilling the posterior wall of the internal auditory canal.

The average distance from the origin to the porus acousticus was reported as 9.7 mm.[27] In the present study, it was measured to be 11.32 mm, and the distance from the porus to the lateral fundus was 8.93 mm. This discrepancy is probably due not only to individual variations but also to racial differences. The dimensions in this study are somewhat longer than those reported in whites. The difference may also be contributed to by the authors' measurement technique, in which we measured the length from the innermost side of the origin, rather than from the portion at which the seventh and eighth cranial nerves begin to parallel each other.

In conclusion, from the above results, the AICA was definitely a branch of the basilar artery, and the IAA was a branch of the AICA. The discrepancies with other studies can be regarded as resulting from different definitions of the IAA. The location of the AICA loop was more commonly medial to the meatus than at or within the meatus in Koreans. Also, the dimension of the eighth cranial nerve was somewhat greater than that of previous reports.

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MALIGNANT HYPERTHERMIA IN THE OTOLARYNGOLOGIC PATIENT: PROSPECTIVE ANESTHETIC AND SURGICAL MANAGEMENT OF EIGHT CHILDREN

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Malignant hyperthermia (MH) is a rare genetic myopathy whose hallmark is rise in body temperature. This hypermetabolic state is triggered by inhalational anesthetics and/or depolarizing muscle relaxants such as succinylcholine. Even the use of dantrolene may not be protective against the hypermetabolic crisis. Eight patients at risk for MH undergoing tonsillectomy, adenoidectomy, and/or myringotomy with ventilation tube insertion were anesthetized with nitrous oxide, barbiturates, opiates, tranquilizers, and nondepolarizing muscle relaxants without dantrolene and without complication. Cardiac monitoring and rectal temperatures were followed. In order to provide additional evidence, all eight patients had vastus lateralis muscle biopsies with subsequent caffeine-halothane contracture studies performed. The contracture study showed positive results in seven of eight patients studied, indicating MH-susceptible muscle. No anesthetic or operative complications were encountered. This study demonstrates that patients at risk of developing MH crisis can have otolaryngologic procedures performed relatively safely while undergoing appropriately selected anesthesia.

KEY WORDS — malignant hyperthermia.

INTRODUCTION

Although the first and second descriptions of malignant hyperthermia (MH) were in 1929[1] and 1960,[2] the term malignant hyperthermia was used in English for the first time in 1966 by Wilson et al[3] and Gordon.[4] Gronert has described MH, an inherited disease, as a hypermetabolic process triggered by inhalational agents and/or depolarizing muscle relaxants such as succinylcholine.[5] This hypermetabolic state is characterized by cardiac rhythm irregularities; rapidly rising fever (to as high as 43°C) as fast as 1°C/min; muscle rigidity; metabolic and respiratory acidosis; and elevated levels of creatine phosphokinase, calcium, myoglobin, and potassium.[6,7] These values are increased because of muscle breakdown, which in turn is caused by increased metabolism.

Considering the fact that 280 of 734 reported hyperthermia crises up to 1983 occurred during head and neck procedures,[8] otolaryngologists may be reluctant to operate on patients who might be at risk. Risk factors include a previous intraoperative MH episode or a family history of MH. To show that such patients can be operated on relatively safely, a prospective study was undertaken in children with either a positive family history or an episode of MH on a previous trip to the operating room. Although dantrolene has been advocated as prophylaxis in the development of MH,[9] there have been two reports that this pretreatment failed to prevent the onset of MH during operation.[10,11] Dantrolene was not used prophylactically in this study. Because stress is known to be a potent factor in production of MH in swine,[12] the patients (all children) were sedated before arrival in the operating room. Although there is some disagreement about the value of muscle contracture studies, each patient had a muscle biopsy done and a muscle contracture test performed.

MATERIALS AND METHODS

Eight patients at risk for MH were identified at the UCLA Medical Center. There were five boys and three girls from 8 months of age to 6 years of age. Risk factors included strong family history of possible prior MH-type reaction (five patients) or previous intraoperative MH (three patients). They underwent tonsillectomy, adenoidectomy, and/or myringotomy with middle ear ventilation tube placement. They were all operated on by one of us (J.P.D.), and anesthesia was administered by another one of us (R.R.).

Anxiety in the preoperative period was minimized by rectal suppositories of barbiturates, and the children were monitored by an anesthesiologist before their arrival in the operating room. Anesthesia lasting 60 to 90 minutes consisted of nitrous oxide, barbiturates, opiates, and nondepolarizing muscle relaxants. Potent volatile agents such as halothane, enflurane, or isoflurane, and the depolarizing muscle relaxants such as succinylcholine were not used. Oxygen and nitrous oxide was administered through a "virgin" anesthesia machine, ie,

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one that had never been exposed to volatile inhalational agents. Because volatile anesthetic agents are soluble in rubber, disposable plastic tubing was used. Throughout the preoperative, intraoperative, and postoperative periods, cardiac monitoring and rectal temperatures were followed. Blood gas analysis was not performed on any of these patients during the operation or postoperatively. Neither oral nor intravenous dantrolene was given prior to induction of anesthesia. None of the patients was given dantrolene during the procedure.

All eight patients underwent vastus lateralis biopsy for use in the caffeine-halothane contracture test as described by Britt et al.[13] The quadriceps muscle segment was approximately 3 x 5 x 20 mm, and it was removed with virtually all longitudinal fibers intact. It was mounted on a Grass force-displacement transducer (Grass Instruments, Quincy, Mass) with a resting tension of 1 g. The muscle strips were placed in an oxygenated Krebs-Ringer bath, and various concentrations of caffeine were applied to the bath. Isometric tension was recorded with a Grass polygraph (Grass Instruments). Tension was defined as the caffeine specific concentration (CSC) for muscle strips exposed to caffeine only. Similar measurements were made with caffeine and halothane, and the result was called the caffeine specific concentration with halothane (CSC-H). Malignant hyperthermia–susceptible skeletal muscle has a CSC of less than 4.0 mmol/L caffeine in a halothane-free environment and a CSC-H of 1.0 mmol/L caffeine in the presence of halothane. The lower the CSC-H number, the more strongly positive is the patient for MH. In this study MH-susceptible muscle was termed caffeine-halothane contracture test–positive.

RESULTS

Eight patients were operated on. Five patients had a family history positive for MH; three patients had a previous episode of MH in the operating room (see Table). Despite risk factors pointing to the possible development of MH during the operations, all patients underwent general anesthesia and operation without developing signs of MH. Preoperative, intraoperative, and postoperative assessment of rectal temperature, cardiac activity, and tactile muscle tension showed no sign of impending MH. No electrocardiographic changes were seen, and none of the patients demonstrated temperature elevation. Seven of the patients had positive halothane contracture test results (see Table). In one patient, an 8-month-old with a positive family history, the test result was negative.

SUMMARY OF MUSCLE BIOPSY RESULTS IN EIGHT PATIENTS UNDERGOING CAFFEINE-HALOTHANE CONTRACTURE TEST

Patient	*Age*	*Sex*	*Risk Factor*	*Caffeine-Halothane Contracture Test**
1	8 mo	M	Positive family history	Negative
2	3 yr	F	Elevated CPK during previous operation	Positive
3	4 yr	M	Positive family history	Positive
4	4 yr	F	Positive family history	Positive
5	5 yr		Positive family history	Positive
6	6 yr	F	Elevated CPK during previous operation	Positive
7	8 yr	M	Positive family history	Positive
8	6 yr	M	Elevated CPK during previous operation	Positive

CPK — creatine phosphokinase.

*Positive result — caffeine specific concentration of less than 4.0 mmol/L in halothane-free medium but caffeine specific concentration of less than 1.0 mmol/L caffeine in presence of halothane.

DISCUSSION

The precise cellular defect responsible for development of MH crisis is unknown. However, it is thought to be an abnormality of the sarcoplasmic reticulum of skeletal muscle that in response to a triggering agent releases an excessive amount of calcium into the myoplasm. Adenosine triphosphate (ATP) provides energy for the calcium pump in an attempt to keep up with this calcium loss.[7] If the calcium pump can maintain calcium balance, the syndrome does not occur. If ATP cannot be provided fast enough, calcium concentration increases in this contractile part of the cell, triggering sustained contraction and blocking relaxation. The net effect is a marked increase in oxygen consumption that generates heat, resulting in an elevated temperature, anaerobic metabolism, and acidosis. Because depletion of ATP prevents membrane-bound active transport systems from maintaining all ionic gradients, potassium, magnesium, and phosphates diffuse out of muscle cells. Cell death ensues, and large amounts of myoglobin are released. Ventricular fibrillation is the usual cause of early death, with pulmonary edema from myocardial failure, renal failure, and brain damage accounting for most late mortalities.[14]

While the diagnosis of MH reaction is suspected clinically by the classic constellation of signs following induction of general anesthesia (muscle rigidity, cardiac arrhythmias, temperature elevation, and myoglobulinuria), in the laboratory, MH-susceptible skeletal muscle is identified by the caffeine-halothane contracture test. Seven of eight patients in this study had CSC-H values that were by convention diagnostic of MH.[15] The patient who had a negative CSC-H test result had a family history of MH. At 8 months of age he was the youngest in this group of patients (see Table), and he had a CSC-H value that was less than that seen in normal patients. It had been demonstrated that patients with a strong family history of MH can have CSC-H values intermediate between those of normal patients and established MH patients.[13]

Unfortunately, no preoperative screening test will identify those patients at risk. Although it would appear that preoperative measurement of creatine phosphokinase levels might offer some help in this area, a series of 121 patients with MH had normal levels.[16]

Management of MH crisis, should it develop, is well standardized and includes discontinuation of anesthetic agents; administration of 100% oxygen; monitoring of temperature, vital signs, arterial blood gases, serum electrolytes, and urine output; cooling; treatment of cardiac irregularities; and the use of intravenous dantrolene. In addition to being utilized during an acute episode, dantrolene, inhibiting release of calcium from sarcoplasmic reticulum, has been used in prophylaxis both orally and intravenously.[17] However, this drug may not prevent a hyperthermic event even when used prophylactically.[10,11] Dantrolene was not used prophylactically in any of these eight patients. Although it will remain a very useful drug in treatment of MH crises and may be used as a prophylactic agent by others, this study shows that MH patients can be anesthetized relatively safely during otolaryngologic procedures without the use of this drug, provided a protocol similar to that delineated in this paper is followed carefully.

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CANCER OF THE TONGUE BASE TREATED BY A TRANSPHARYNGEAL APPROACH

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Tongue base resection plays an important role in the management of the patient with cancer of the posterior tongue. The considerable morbidity resulting from loss of functional tongue includes compromised deglutition, chronic aspiration, and altered speech articulation. The particular operative approach used dictates additional secondary morbidity, which may include cosmetic and functional defects of the mandibular arch, malocclusion, lip and chin scars, and postoperative changes in the oral cavity. Our recent experience with a transpharyngeal approach in 13 patients with tongue base cancer is reviewed. Adequate operative exposure was obtained in all cases. Persistent aspiration was not a problem, and all patients learned to swallow effectively. The transpharyngeal approach avoids unnecessary surgical trauma to the mandible and anterior oral cavity and minimizes cosmetic deformity. Our early experience with this approach is encouraging.

KEY WORDS — aspiration, mandibular integrity, pharyngotomy, supraglottic laryngectomy, tongue base cancer.

INTRODUCTION

Surgical therapy plays an important role in the management of patients with cancer of the posterior tongue. The morbidity resulting from extirpative procedures in the base of tongue region consists of compromised deglutition, altered speech articulation, and chronic aspiration. Tongue resection not only reduces tongue bulk, but may markedly impair the mobility of the remaining tongue musculature. This often results in impaired articulation and dysphagia, particularly through the oral phases of deglutition.[1] Resection of the tongue base also predisposes to aspiration, because the food bolus cannot be propelled cohesively into the hypopharynx, and thereby falls into the laryngeal inlet.[2] The particular operative approach used for exposure of the tongue base dictates additional secondary morbidity that may include cosmetic and functional defects of the mandibular arch, malocclusion, lip and chin scars, and postoperative changes in the oral cavity.

The transmandibular approach for resection of tongue base tumors is the method usually employed by most clinical authorities.[3-6] Mandibulectomy usually provides the widest possible operative exposure, with the disadvantages of cosmetic and functional deformity.[4] Cheek depression results from loss of the hemimandible and adjacent soft tissue. This deformity is compounded when primary closure is accomplished by suturing the buccal mucosa to the tongue. Mandibular retrusion and chin deviation toward the side of resection result from the unopposed pull of the pterygoid muscles on the side opposite the mandibulectomy combined with wound contracture. Severe malocclusion and subsequent inability to effectively masticate food often result.[4] The lip-splitting incision has been advocated in mandibulectomy for lesions in the oropharynx, but results in lip and chin scars.[7,8] To reduce the severity of these sequelae, the routine use of intermaxillary fixation to avoid malocclusion and the visor-flap technique to avoid facial scars have been advocated.[4]

A trend toward the use of mandible-sparing procedures has been observed in the surgical management of tongue tumors.[5] Stepped mandibulotomy may be combined with transoral or transpharyngeal resection of the tongue base to preserve the mandibular arch.[3,9] Intraosseous wires or stainless steel plates are then used to approximate the proximal and distal mandibular segments. Disadvantages of this technique include increased operating time and concern for nonunion and osteomyelitis, particularly in patients likely to undergo postoperative radiotherapy. Median labiomandibular glossotomy has been used for resection of midline tumors of the tongue base.[10] In this procedure, the lip and mandible are split in the midline and a midline glossotomy is performed to the anterior margin of resection of the tongue base. Although a lip scar results, mandibular continuity is preserved. This approach is suitable for benign tumors and low-grade salivary gland malignancies of the tongue base. Only carefully selected small squamous cell carcinomas may be approached in this manner.[10]

During the past 6 years we have employed a transpharyngeal approach for selected tongue base cancers. We have found this operative approach very satisfactory from the standpoint of operative exposure, and it allows the maximum preservation of speech, swallowing, and cosmesis without sacrifice of mandibular function.

MATERIALS AND METHODS

The records of 13 patients with tongue base cancer treated by a transpharyngeal approach were reviewed. All surgical procedures were performed under the direct supervision of the senior author

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(T.C.C.), who also followed the patients postoperatively.

Preoperative evaluation emphasized careful visualization and palpation of the oropharynx to determine the anterior and lateral extent of the tumor. This was corroborated by computed tomography and/or magnetic resonance imaging, with the latter being somewhat more helpful in the assessment of the depth of tumor invasion into the tongue root. Final determination of tumor extent was performed under general anesthesia employing bimanual palpation and direct laryngoscopy immediately prior to surgical excision. If the tumor was posterior to the circumvallate papillae, this approach was employed. Tumor extent inferiorly into the bottom of the vallecula or the epiglottis required a supraglottic laryngectomy. Not included in this series were patients with extensive laryngeal involvement who required total laryngectomy.

If the tongue base tumor extended laterally to involve the mandible or tonsillar fossae, a transmandibular approach was substituted for a transpharyngeal approach.

OPERATIVE APPROACH

All patients underwent a unilateral cervical lymph node dissection on the side of the lesion with preservation of the spinal accessory nerve unless the nerve was directly involved with tumor. No patient required bilateral cervical node dissection.

The external approach through the pharynx and/or larynx depended on the preoperative assessment of the anatomic extent of the tumor. In the majority of patients the tumor extended sufficiently low into the vallecula that a horizontal resection of the upper portion of one or both thyroid laminae was necessary to adequately clear the tumor inferiorly. The perichondrium of the lamina was preserved by the same method employed in a conventional supraglottic laryngectomy. The pharyngotomy site was carefully selected to ensure an ample margin for tumor resection, then gradually enlarged to allow direct visualization to the tongue base and larynx for all mucosal incisions.

Usually, the inferior portion of the resection was performed first. In five patients the inferior resection necessitated complete resection of the epiglottis, usually sparing the false vocal cords. Another six patients had partial resection of the epiglottis. In these patients the epiglottic remnant was transposed laterally to create a hood over the laryngeal inlet as described in a previous publication by the senior author.[2] In the remaining two patients the epiglottis was preserved and the inferior resection margin was at the epiglottic-lingual sulcus. Almost always it was necessary to resect a portion of the hyoid bone. The hyoid bone and its attaching muscles opposite the tumor were preserved to maintain laryngeal support. The superior laryngeal nerves were preserved whenever possible to maintain sensory innervation of the larynx.

The anterior aspect of the resection was carried out last. Visualization was enhanced by downward traction of the tongue into the operative field by suture or clamps and upward traction of the mandible. Through the enlarged pharyngotomy opening the nasopharynx was easily visualized. This exposure permitted resection of the lateral pharyngeal wall to the midtonsillar level. In all patients the hypoglossal nerve was preserved on the side opposite the tumor. In many patients the ipsilateral hypoglossal nerve was also preserved by dissection and elevation of the nerve to maintain innervation of the anterior tongue. The lingual nerve could usually be spared because of its anterior location.

The type of wound closure depended on the size of the defect. In 10 patients the defect was repaired by use of a method similar to that employed in supraglottic laryngectomy. With use of this technique, lateral closure was accomplished by approximating the mucosa of the pharyngeal wall to the mucosa of the lateral tongue base. Since mucosal approximation is not possible, anterior repair was accomplished by suturing the laryngeal perichondrium and infrahyoid musculature to the remaining tongue base with 2-0 absorbable interrupted sutures. By placing the sutures deep in the ventral tongue base, the larynx was suspended anteriorly and superiorly.[11] In three patients with larger defects involving the lateral pharyngeal wall and tongue base, a pectoralis myocutaneous flap was employed in the repair. In one patient the epiglottis was preserved entirely, and in two patients the lateral third of the epiglottis was resected. The skin portion of the myocutaneous flap was sutured directly to the pharyngeal wall mucosa and tongue base mucosa. The bulkiness of the pectoralis myocutaneous flap was not a problem, because the defect was never circumferential. In fact, the defect rarely exceeded half of the oropharyngeal circumference.

The tracheostomy tube cuff remained inflated for the first 72 hours postoperatively until the patient could adequately cough and perform tracheal hygiene. Nasogastric tube feedings were usually maintained after hospital discharge and frequently throughout the entire period of postoperative radiotherapy. A small-bore pediatric nasogastric feeding tube was maintained during the initial period of swallowing rehabilitation and was removed once adequate oral intake was assured. The tracheostomy tube was typically removed after radiotherapy when it was determined that irradiation edema would not obstruct the laryngeal airway.

RESULTS

The Table depicts case summaries for the 13 cases reviewed. Mean age was 63 years, with a range of

CASE SUMMARIES

Pt	*Sex*	*Age*	*Tumor*	*Operation*	*Complications*	*Outcome*
1	F	80	T2N0M0	TBR, CND	—	DOD 5 yr
2	M	56	T1N1M0	TBR, CND	—	NED 5.5 yr
3	F	70	T2N1M0	TBR, CND	—	NED 3 yr
4	M	69	T3N0M0	TBR, CND	P-C fistula	NED 3 yr
5	F	56	T3N0M0	TBR, CND	Wound slough	DOD 15 mo
6	F	53	T3N0M0	TBR, CND	—	NED 14 mo
7	M	66	T3N0M0	TBR, CND, PMC	—	<6 mo F/U
8	M	54	T2N1M0	TBR, CND	—	NED 32 mo
9	M	69	T3N0M0	TBR, CND	P-C fistula	NED 3 yr
10	F	59	T2N2aM0	TBR, CND, PMC	—	NED 2 yr
11	M	57	T2N2aM0	TBR, CND	P-C fistula	NED 2.5 yr
12	M	65	T2N2aM0	TBR, CND, PMC	P-C fistula	NED 14 mo
13	F	64	T3N2aM0	TBR, CND	P-C fistula	NED 27 mo

TBR — tongue base resection, CND — cervical node dissection, PMC — pectoralis myocutaneous flap, P-C — pharyngocutaneous, DOD — dead of disease, NED — no evidence of disease, F/U — follow-up.

53 to 80. There were seven men and six women. The most common presenting symptom was sore throat, although four patients complained of an asymptomatic neck mass. None of the patients had disease anterior to the circumvallate papillae. Nine patients presented with stage III disease, and four with stage IV disease.[12] Histologically, seven tumors were moderately differentiated epidermoid carcinoma, two were moderately to poorly differentiated epidermoid carcinoma, and four were poorly differentiated epidermoid carcinoma. Pathologically confirmed ipsilateral cervical metastases were present in 11 patients. Two patients had microscopically positive deep-muscle margins. Postoperatively, 11 patients received full-course external beam radiotherapy to the primary site and to both sides of the neck.

The pharyngocutaneous fistulas that occurred in five patients were treated conservatively with local care and intravenous antibiotics. Wound slough occurred in a sixth patient, requiring a pectoralis myocutaneous flap for carotid artery coverage. One patient developed an aspiration pneumonia that prolonged hospitalization. Osteomyelitis of the sternoclavicular joint occurred in a patient with a pharyngocutaneous fistula and required readmission for operative debridement and prolonged intravenous antibiotic therapy. There were no perioperative deaths.

Decannulation of the tracheostomy tube was accomplished in all patients at a mean interval of 3 months. All patients were discharged from the hospital with a small indwelling nasogastric tube for supplemental alimentation while they practiced swallowing. This was removed within 1 month in most patients; however, one patient required supplemental feedings for 12 months before a soft diet could be adequately tolerated. No patient required completion laryngectomy for intractable aspiration. Although an objective assessment of speech articulation was not performed, all patients ultimately developed readily understandable speech.

A minimum 2-year follow-up was available in 10 patients, of whom 8 are alive and free of disease (80%). Two patients have died of recurrent disease, after 15 months and 5 years of follow-up.

DISCUSSION

Cancer of the tongue base remains a poorly controlled disease entity. Despite advances in surgical and radiotherapeutic techniques, a reported survival rate of 35% to 45% has not improved significantly in the past 40 years.[13-15] Tumors of the tongue base are usually diagnosed at an advanced stage because of a lack of symptoms and a paucity of physical findings.[7] Epidermoid carcinomas of the pharyngeal tongue tend to be clinically aggressive because of the rich lymphatic network of the oropharynx and a tendency toward a poor histologic differentiation.[16] Sixty percent to 75% of patients will have clinically positive ipsilateral or contralateral cervical nodes at the time of initial visit.[7] Seventy-seven percent of 54 patients with tongue base cancer reported by Iidstad et al[13] had stage III or IV disease on initial presentation. Patients with advanced disease usually require combined therapy consisting of surgical treatment and irradiation. As a result of the expected morbidity associated with tongue base resection, however, the majority of patients with tongue base cancer opt for primary radiotherapy as the sole treatment modality.

A transpharyngeal approach to the tongue base would reduce this anticipated morbidity, particularly those sequelae related to exposure of the tongue base by a transmandibular route. Whicker et al[17] have criticized the transpharyngeal approach because of the lack of exposure, to which they attributed a high incidence of local recurrence. In the present series we never felt that the exposure was limited. By first exposing the tumor inferiorly and continuing the dissection superiorly into the oropharynx, all perimeters of the tumor could easily be visualized, particularly with posterior rotation of the tongue. Although the results are not long-term, our 2-year disease-free rate of 80% compares favorably with those of other series.[7,14,17]

It is well known that resection of the tongue base hampers swallowing and predisposes to aspiration. This is aggravated when supraglottic structures are also sacrificed. Because of severe aspiration, tongue base cancers that deeply infiltrate the vallecula or supraglottis frequently necessitate total laryngectomy. Weisburger and Lingeman[18] proposed a modified supraglottic laryngectomy with partial glottal closure in cases of tongue base cancer that would otherwise have required total laryngectomy to prevent aspiration. They felt that the approach was adequate for resection of these large tumors extending to involve the lateral pharyngeal walls. By suturing the false vocal cords together, a sphincter was created, preventing aspiration. However, none of the patients was ever decannulated. In the present series, partial supraglottic laryngectomy was performed in all patients. By maximal preservation of laryngeal sensory innervation, preservation of infrahyoid musculature, dissection and preservation of hypoglossal nerves, and suspension of the larynx, important physiologic barriers to aspiration were maintained. These patients are capable of learning deglutition without significant aspiration.

Rehabilitation for deficits in swallowing and speech is an important adjunct in the postoperative care of these patients. We use a team approach, involving the head and neck surgeon, speech therapist, swallowing therapist, and oral/maxillofacial prosthodontist. Nasogastric tube feedings supplement the oral feedings postoperatively while the patient learns to swallow. The palatal augmentation prosthesis has been used in one case to reduce the free space between the palate and tongue remnant. Improved linguopalatal contact allows stronger lingual propulsion during deglutition and better articulation during speech.[1] The desire for improved oral performance emphasizes the need to restore mandibular and occlusal relationships to an optimal functional state.

On the basis of this experience we believe that a transpharyngeal approach is the best surgical method for selected base of tongue cancers. While providing ample operative exposure, the transpharyngeal approach maintains mandibular and occlusal integrity, avoids cosmetic deformity, and prevents scarring in the anterior oral cavity for maximal mobility of the tongue remnant.

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ANOMALY OF THE HYPOGLOSSAL NERVE: EMBRYOLOGIC, ANATOMIC, AND SURGICAL CONSIDERATIONS

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An anomaly of the hypoglossal nerve was discovered during a procedure to anastomose the 12th and 7th cranial nerves. This anomaly is described, and an embryologic mechanism is proposed to explain the occurrence of this particular anomaly. The surgical anatomy of the hypoglossal nerve is reviewed, and reasonable approaches to the surgical identification of the hypoglossal nerve are discussed.

KEY WORDS — anomaly, cranial nerves, hypoglossal nerve.

INTRODUCTION

A variety of surgical procedures require precise knowledge of the course of the 12th cranial nerve. Standard anatomy texts provide basic information to help the surgeon locate the nerve and avoid debilitating injury to it. At times, however, the nerve might not be in the "textbook" location, as illustrated by the following case history. The possible embryologic origin of this anomaly is discussed, the surgical anatomy is reviewed, and a reasonable approach to finding the hypoglossal nerve, based on sound anatomic principles, is proposed.

CASE REPORT

A 62-year-old man was admitted to Shadyside Hospital of Pittsburgh in 1987 to undergo a procedure to anastomose the 7th to the 12th cranial nerve. One year earlier the patient had undergone excision of an acoustic neuroma that resulted in total left-sided facial paralysis. At the time of the surgical exploration of the left side of the neck reported in this paper, the vertical descending segment of the 12th cranial nerve could not be found in its usual position under the posterior belly of the digastric muscle, although the 9th, 10th, and 11th cranial nerves were identified in their normal positions. Since the vertical segment of the 12th nerve was not found, the neck incision was extended caudally, and the descendens hypoglossi was found along the lateral surface of the carotid artery. This was followed cephalad to the 12th nerve, which was found to have been drawn out of its natural position by a branch from the lingual artery. This arterial branch, which serves the thyrohyoid muscle, had looped around the nerve and folded below the digastric tendon at the cornu of the hyoid bone (Fig 1). Once located, the 12th nerve was followed superiorly to the point at which it fused with the vagus nerve high in the neck. The 12-7 anastomosis was then completed.

EMBRYOLOGY

A possible mechanism for the anomalous position

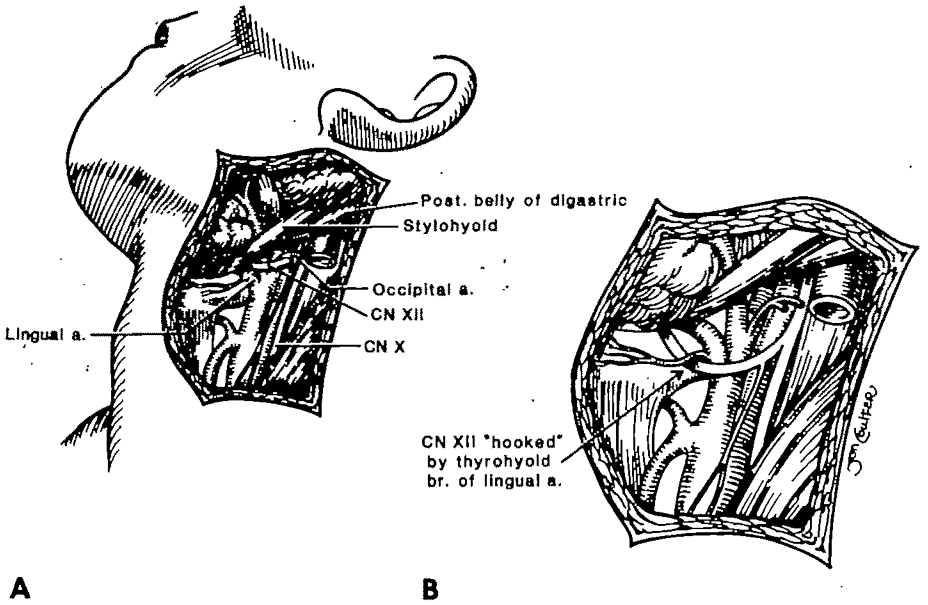

Fig 1. Course of hypoglossal nerve (CN XII). A) Typical course. B) Anomalous course: nerve was drawn inferiorly by thyrohyoid branch of lingual artery.

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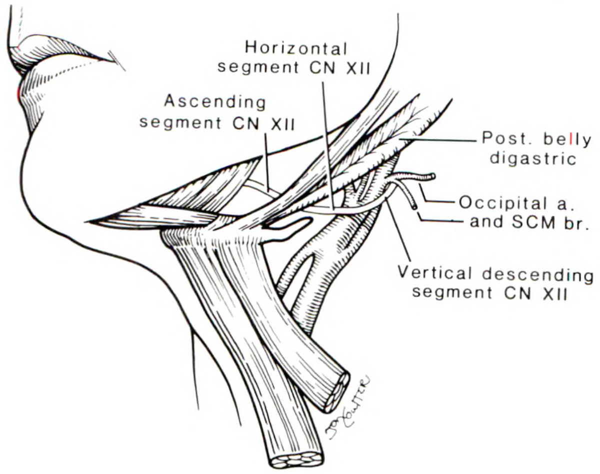

Fig 2. Vertical descending, horizontal, and ascending segments of hypoglossal nerve. SCM br. — sternocleidomastoid branch.

of the hypoglossal nerve in this case may be alteration in the normal process of ascent of the cranial nerves in the neck during embryogenesis.[1] As the developing cranial nerves ascend in the neck, their final positions are modified by the disappearance of the primitive arteries. The developing 12th cranial nerve passes toward the tongue musculature lateral to the branchial arch arteries. In normal development the hypoglossal nerve moves superiorly, until it reaches the level of the occipital artery.[2] In the present case the anomalous course of the thyrohyoid branch of the lingual artery may have prevented the ascension of the hypoglossal nerve to its normal position.

ANATOMY

The course of the hypoglossal nerve can be divided into vertical descending, horizontal, and ascending segments (Fig 2).

The anatomic relations of the vertical descending portion of the hypoglossal nerve are relatively constant. Hollinshead[3] notes that the 12th cranial nerve emerges from the hypoglossal canal medial to the internal jugular vein and the carotid artery. It runs laterally and inferiorly to lie behind the tenth nerve, then courses more inferiorly to pass between the internal jugular vein and the internal carotid artery. In 8% of individuals the 12th nerve passes behind the internal jugular vein.[3] Another variation is that the nerve may be fused by fibrous adhesions to the nodose ganglion of the 10th nerve in its vertical segment. The 12th nerve then travels deep to the posterior belly of the digastric muscle, and over the internal carotid artery. Curto et al[4] have described the anatomic relations of the vertical segment of the hypoglossal nerve.

The horizontal segment of the hypoglossal nerve begins where it is crossed by the occipital artery. This segment can demonstrate two important variations. The first is in the relationship of this nerve to the branches of the external carotid artery. Nathan and Levy[2] studied 25 cadaver dissections and found three main positions of the 12th nerve relative to the occipital artery (Fig 3). In type 1 (Fig 3A) the occipital artery arose from the external carotid artery superior to the hypoglossal nerve and ran posteriorly to cross the nerve superficially. This variation was seen in 37% of their 25 cases. In 20% of their cases the occipital artery arose at the same level as the 12th nerve (Fig 3B). Finally, in 41% of the cases they studied, the occipital artery arose below the level of the hypoglossal nerve, then ran superiorly and looped posteriorly around the nerve (Fig 3C). Imparato et al[5] found that the hypoglossal nerve was most commonly looped by the sternocleidomastoid branch of the external carotid artery and its accompanying vein. A number of anatomic texts[3,6,7] state that the nerve is crossed by the sternocleidomastoid artery, which branches from the occipital artery. Nathan and Levy[2] found that the 12th nerve was looped by the sternocleidomastoid artery in one of 40 dissections.

The second major anatomic variation in the horizontal segment of the hypoglossal nerve is the point at which the 12th nerve crosses the carotid bifurca-

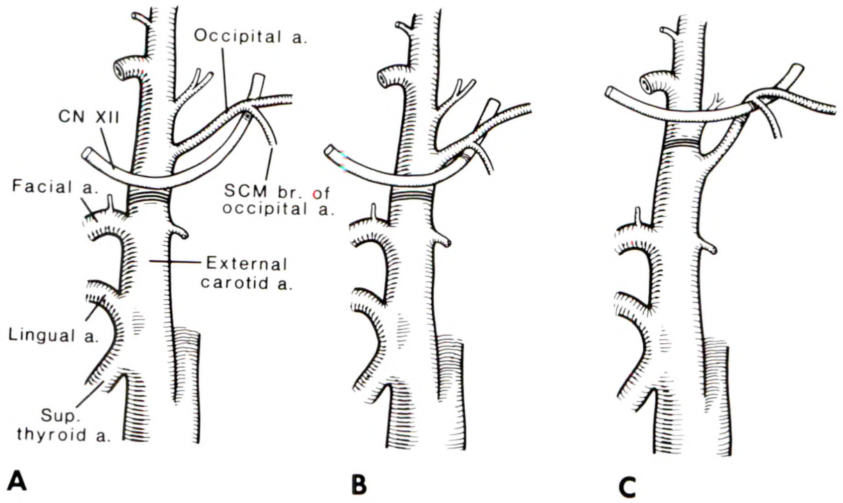

Fig 3. Three most common relations of hypoglossal nerve (CN XII) to occipital artery. A) Nerve crossing inferior to origin of artery. SCM br. — sternocleidomastoid branch. B) Nerve crossing at origin of artery. C) Nerve crossing above origin of artery. Despite this variation in where nerve crosses artery, occipital artery usually loops over hypoglossal nerve during nerve's embryologic ascent in neck.

tion. Curto et al[4] found that 98 of 110 12th nerves crossed 1 cm above the bifurcation, with a range of 0 to 3.5 cm above the bifurcation. Eleven of 110 nerves crossed the bifurcation, and one crossed 1 cm below the bifurcation. The horizontal segment ends as the nerve passes anterior to the deep tendon of the posterior belly of the digastric muscle.

The anatomy of the ascending portion of the nerve is relatively constant. Traveling anteriorly, the nerve forms the superior leg of Lesser's triangle.[3] The remaining limbs of the triangle are the anterior and posterior bellies of the digastric muscle. The lingual artery courses in this triangle, deep to the hypoglossal nerve, and travels medial to the hypoglossal muscle to enter the muscular substance of the tongue. The lingual vein (vena comitans nervi hypoglossi) continues to course with the hypoglossal nerve over the lateral surface of the hypoglossal muscle. Then both the vein and the 12th nerve run deep to the posterior border of the mylohyoid muscle, before curving forward and upward on the lateral surface of the genioglossus to enter the tongue muscles.

SURGICAL CONSIDERATIONS

A number of head and neck procedures require that the hypoglossal nerve be identified and protected from injury: hypoglossal-facial nerve anastomosis, submandibular gland excision, radical or modified neck dissection, carotid endarterectomy, and supraglottic or total laryngectomy. At times the vertical segment of the hypoglossal nerve may be obscured by posterior displacement behind the internal jugular vein or adhesions to the nodose ganglion of the 10th nerve. Embryologic and anatomic studies have shown that the hypoglossal nerve is found caudal to the occipital artery. A sound approach to locating the nerve inferiorly in the neck is to identify the descendens hypoglossi.

The case reported in this paper shows the importance of being aware of the presence of the 12th nerve during a total or partial laryngectomy procedure; clearly, the nerve in this case might easily have been damaged in a laryngeal procedure because of its proximity to the hyoid bone.

During submandibular gland excision, the removal is begun along the inferior portion of the gland. During dissection of the intermediate tendon of the digastric muscles, the hypoglossal nerve will be exposed. As discussed previously, the location of the hypoglossal nerve superior to the digastric tendon is relatively constant. Care should be taken to identify and protect the 12th nerve during this procedure.

A common complication of carotid endarterectomy is hypoglossal palsy due to superior retraction of the 12th nerve to visualize the carotid bifurcation. Imparato et al[5] have proposed that the 12th nerve be freed superiorly by dissecting the descendens hypoglossi and sectioning the vascular structures that cross the nerve. They have found that the sternocleidomastoid branch of the occipital artery and its accompanying veins hold the nerve caudally. Others[2] have found that the occipital artery itself more commonly loops over the 12th nerve.

Finally, it is important to remember that during the vast majority of neck explorations or neck dissections, the hypoglossal nerve will be found to cross approximately 1 cm above the carotid bifurcation.

CONCLUSION

This case, in which the thyrohyoid branch of the lingual artery hooked the hypoglossal nerve at the level of the hyoid bone, is evidence that the horizontal segment of the hypoglossal nerve may vary widely in anatomic location. It is likely that in this case the 12th nerve was held caudally during its embryologic ascent in the neck. The surgeon should be aware that anatomy atlases may not always show the most common variations of a structure, nor may anatomy texts point out all variations. To protect anatomic structures, the surgeon should expect variability and allow for it, realizing that perhaps the most constant aspect of human anatomy is its inconstancy.

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LERMOYEZ'S SYNDROME: HISTOPATHOLOGIC REPORT OF A CASE

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This paper reports findings in a pair of temporal bones from a patient with clinical evidence of Lermoyez's syndrome, a rare variant of Meniere's disease. Endolymphatic hydrops is limited to the basal turn of the cochlea and saccule in Lermoyez's syndrome, but more generalized in Meniere's disease.

KEY WORDS — endolymphatic hydrops, Lermoyez's syndrome, Meniere's disease.

LITERATURE REVIEW

Lermoyez[1,2] in 1919 was the first to describe the rare variant of Meniere's disease that now bears his name. Symptoms are the same as in Meniere's disease but in reverse order: tinnitus and progressive hearing loss precede an attack of vertigo and then subside after the vertigo has become established.

Lermoyez attributed the condition to a spasm of the internal auditory artery and its subsequent release. Later, Portmann,[3] Williams,[4,5] and Bailie[6] accepted this hypothesis. Mygind[7,8] suggested that the cause of the disease was a sudden increase and reduction of pressure in the endolymphatic space. Eagle[9] believed the cause was allergy. Atkinson[10] said it was a sensitivity of the histamine that caused dilation of the capillaries and increased permeability of their walls, which resulted in edema.

CASE REPORT

A 60-year-old man complained of episodes of tinnitus and hearing loss in his right ear that subsided almost completely after attacks of vertigo, nausea, and vomiting. The attacks occurred about once a year for 18 years before his death.

Repeated audiograms showed fluctuating sensorineural hearing loss in the right ear. The fluctuation was primarily in the low frequencies. The loss fluctuated between 33 and 50 dB in the speech frequencies. There was also a nonfluctuating loss of 50 dB at 4 kHz. Speech discrimination varied from 96% to 68%. Hearing remained normal in the left ear except for 4 kHz, at which level it was the same as in the right ear (50 dB) until 3 years prior to death, when he developed symptoms in and from the left ear, and hearing dropped to 38 dB in the speech frequencies.

Petrous pyramid radiographs were normal bilaterally. The results of electronystagmographic examination were essentially normal.

HISTOPATHOLOGIC EXAMINATION

METHOD

The temporal bones were removed about 10 hours after the patient's death, placed in formaldehyde, decalcified in Versene, and embedded in celloidin. The specimens were sectioned in the horizontal plane at a thickness of 20 μm, and every 10th section was stained with hematoxylin and eosin.

RESULTS

Right Ear. Dilation of Reissner's membrane was restricted to the basal turn (see Figure, A). There were two ruptures and consequent outpouchings, one in the posterior part and one in the anterior part (see Figure, B). Outpouchings are believed to occur because the membrane that forms in the defect as healing occurs is thinner than Reissner's membrane and thus less resistant to the consistently increased endolymphatic pressure. They appear as apparent duplications of Reissner's membrane in the scala vestibuli (see Figure, B,C).[11] The saccule also was greatly dilated. The saccular membrane pressed against the footplate and extended into the nonampullated end of the lateral semicircular canal.

We also examined the organ of Corti and the stria vascularis. Although there is some postmortem change, we can estimate the cochlear contents. There is an 80% loss of ganglion cells in the base of the modiolus. The stria vascularis was about 20% atrophic — more in the apex and above the area of rupture.

Left Ear. Examination of the left ear shows hydrops limited to the saccule. Rupture of the anterior inferior portion of the saccule is evidenced by a

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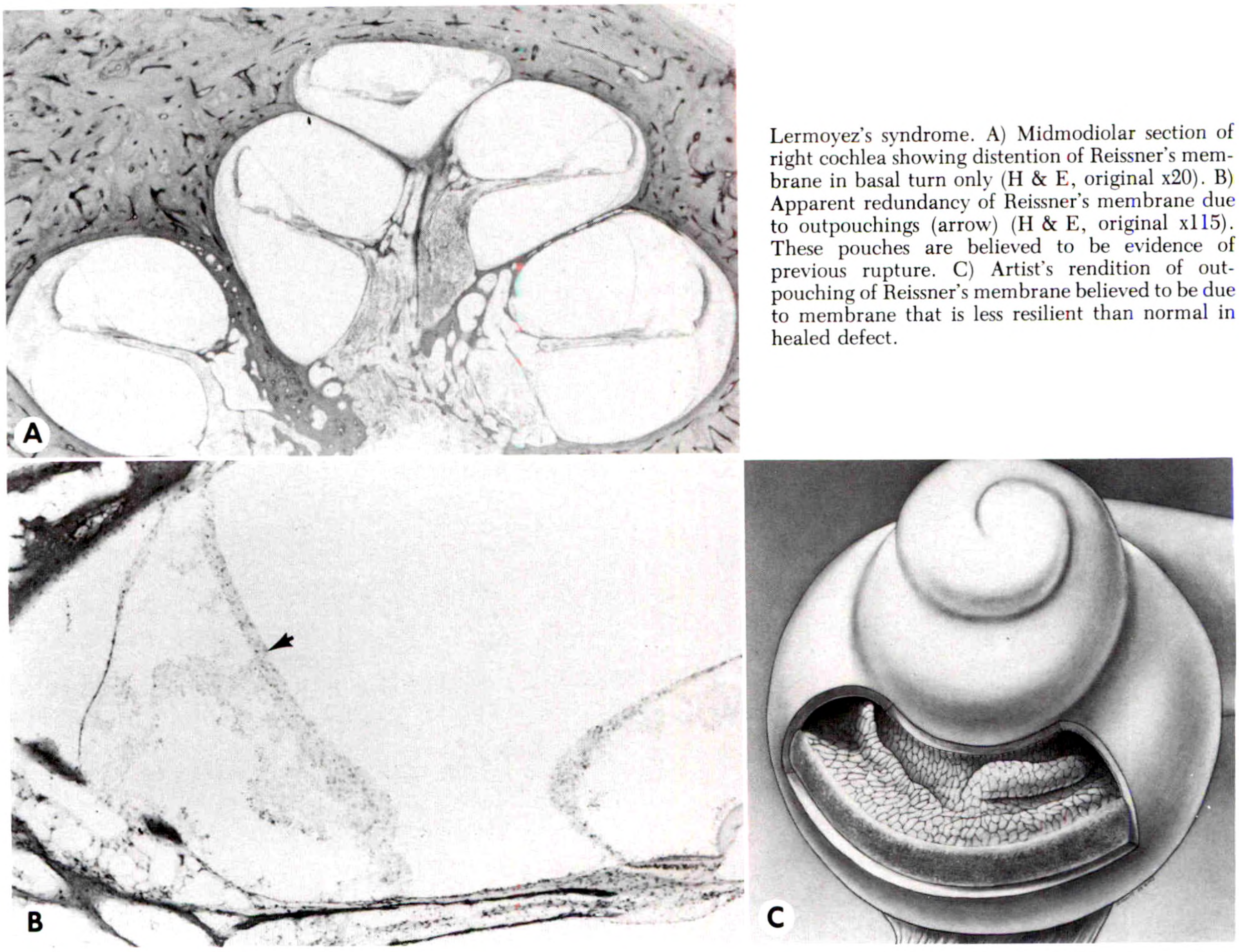

Lermoyez's syndrome. A) Midmodiolar section of right cochlea showing distention of Reissner's membrane in basal turn only (H & E, original x20). B) Apparent redundancy of Reissner's membrane due to outpouchings (arrow) (H & E, original x115). These pouches are believed to be evidence of previous rupture. C) Artist's rendition of outpouching of Reissner's membrane believed to be due to membrane that is less resilient than normal in healed defect.

thin-walled outpouching that extends from the orifice of the ductus reuniens anteriorly to the scala tympani. Its medial surface lies upon the prominence of the ductus reuniens.

DISCUSSION

The interesting finding in the right temporal bone is the local endolymphatic hydrops with rupture and outpouching near the vestibule, and in the left ear a rupture of the saccular membrane. This is the area in which House[12] speculated that hydrops and rupture occur in Lermoyez's syndrome. Whether the limited area of membranous distribution, in or near the vestibule, is related to the difference in the symptoms of Meniere's disease and Lermoyez's disease is open to speculation.

The usual Meniere's history is fluctuating low tone hearing loss, low-pitched tinnitus, a pressure feeling in the ear, and, from time to time, an attack of vertigo accompanied by an increase in tinnitus and a temporary, further decrease in the hearing.

Individuals with Lermoyez's syndrome, on the other hand, report a gradual decrease in hearing and increase in tinnitus, both of which improve with the onset of dizziness. Most patients with Meniere's disease, during an exacerbation of their condition, report attacks of vertigo as being rather frequent. Conversely, the patient in this article experienced attacks about once yearly over 18 years.

Histologically, the difference appears to be in the areas of distention and rupture of Reissner's membrane. In Meniere's disease this may occur throughout the cochlea and in the saccule. In the present case, the ruptures were limited to the upper basal turn and saccule. Reissner's membrane was in its normal position in the rest of the cochlea in the right ear. In the left ear, there was a rupture in the saccule and a normal cochlear duct.

CONCLUSION

The temporal bone findings of a case of Lermoyez's syndrome are presented, indicating abnormalities of the inner ear membranes limited to an area in or near the labyrinth.

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GOBLET CELL DENSITY IN NASAL POLYPS

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The goblet cell density was determined in 29 nasal polyps from 22 patients by use of the periodic acid Schiff–alcian blue whole-mount method. The distribution of goblet cells was found to be extremely irregular, ranging from areas completely devoid of goblet cells to areas with a relatively high density. The median density varied from 280 cells/mm² to 10,000 cells/mm². The total median density for all 15 polyps located anteriorly in the nose was 3,450 cells/mm², compared with 6,050 cells/mm² for 14 posteriorly located polyps. The density was highest in pseudostratified, cylindric epithelium, although great variations occurred among the different areas with this type of epithelium. The goblet cell density may be influenced by several factors, such as the airflow, type and thickness of the epithelium, and whether the genesis of the nasal polyps is infectious or allergic, in addition to polyp growth, size, and age.

KEY WORDS — goblet cells, nasal polyps.

INTRODUCTION

Many studies on the histology of nasal polyps have described the epithelium as being a typical respiratory airway epithelium, ie, a pseudostratified cylindric epithelium with numerous ciliated cells and goblet cells.[1-6] Stratified squamous epithelium has been found on the most anteriorly located polyps. This type of epithelium is considered to be predominant, particularly in those parts of the polyp that are most exposed to the airflow. Some authors have found other types of epithelium in places on polyps, such as transitional forms, as are also found in the bladder.[2,7,8]

This study forms part of our basic research on the mucus-producing elements in the upper and lower respiratory tract under normal and pathologic conditions. In this study we have focused on determining the density of goblet cells in the epithelium of the polyps. Our objectives have been to elucidate whether there are fundamental differences in the density of goblet cells here compared with that found in the respiratory airway epithelium in the nose and sinuses, and to determine whether there are differences in density between anterior and posterior polyps and between proximal and distal segments of the individual polyp.

Our previous analyses have shown the density of goblet cells on both septum[9] and concha[10] to be higher in the posterior than in the anterior location and to be higher on the inferior concha than on the medial concha. The density of goblet cells was considerably higher in the maxillary sinus than in the frontal, ethmoid, and sphenoid sinuses,[11] where the density was lower than in most places on the conchae. The results indicate that the variations in goblet cell density between the different segments of the upper respiratory tract cannot be attributed to the airflow alone; other factors, mostly unknown, must be influential, too.

The literature contains no reports on goblet cells in nasal polyps, although some reports on polyp histology mention their existence.[1-8] Nasal polyps are pathologic formations whose growth causes an increase in the area of the epithelium. At the same time the growing epithelium is exposed to a variety of stimuli such as the airflow and infections, in addition to the original disease responsible for their formation. Therefore, some variation in the goblet cell density in nasal polyps must be expected as compared with that found in the epithelium of the normal nose and sinuses. A thorough study of these aspects may throw light on the behavior of the goblet cells as well as on the respiratory airway epithelium under pathologic conditions, in addition to contributing to our knowledge of the genesis of the nasal polyps, which also is not fully understood.

MATERIAL AND METHODS

The study material comprised 29 nasal polyps from 22 patients; six patients had allergy as the prevailing symptom, six patients had recurrent sinusitis, and ten patients were without known allergy or recurrent sinusitis. Sixteen patients were previously subjected to polyp removal. Of the 29 polyps, 15 (from 14 patients) were located anteriorly in the nose. In one case anterior polyps were taken from both sides of the nose. The remaining 14 polyps were situated behind the anterior ones and were taken from eight other patients (two anterior polyps from one patient). Two posterior polyps from two patients were examined, and from four patients both a posterior and an anterior polyp were examined (Tables 1 and 2). On removal, only the anteriormost polyps were separated from the others, while the remaining, posterior polyps on

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TABLE 1. GOBLET CELL DENSITY IN 15 ANTERIORLY SITUATED NASAL POLYPS

Pt No.	Goblet Cells per 0.01768-mm^2 Field												
	Horizontal Lines Median			Vertical Lines Median			All Countings				Counted Fields		
	Proximal	Middle	Distal	Left	Middle	Right	Median	Range	95% Confidence Limits	25th-75th Percentiles	Total No.	Fields Without Goblet Cells No.	Fields Without Goblet Cells %
1	3	25	168	39	202	144	136	1-247	48-178	25-178	82	0	0
2	101	107	67	54	96	113	92	0-221	83-107	62-125	164	1	1
3	—	—	148	23	38	118	42	3-200	10-172	17-172	22	0	0
4	74	101	47	78	101	85	86	0-193	75- 97	43-120	177	8	5
5	7	7	84	27	35	104	38	0-160	36- 75	11- 86	67	7	11
6	17	51	5	40	—	34	31	0-231	8- 42	5- 60	41	5	12
7	32	16	49	7	3	24	13	0-208	6- 32	2- 91	76	11	15
8	78	123	85	72	144	48	97	0-225	52-112	32-164	90	3	3
9	9	101	141	19	10	38	61	0-201	19- 99	8-125	84	11	13
10	184	126	—	166	127	—	147	11-211	107-170	92-179	45	0	0
11L	0	46	34	24	0	22	13	0-163	5- 29	0- 36	116	35	30
11R	71	106	54	115	118	30	88	0-231	71-103	38-120	113	9	8
12	27	84	4	149	4	53	38	0-217	8- 73	0-123	103	29	28
13	62	33	106	39	39	8	23	0-125	24- 81	16- 99	46	4	9
14	35	86	85	70	93	128	92	0-192	69-118	46-133	81	5	6
Interindividual median	34	85	76	40	66	43	61	13-147	23- 92	31- 92	82	5	8

that side were fixed together, and no record was made of their position in the nose (ie, the posterior polyps were sampled at random).

After fixation in formalin-alcohol, each polyp was cut along the longitudinal axis into two halves, one of which was stained according to the periodic acid Schiff–alcian blue whole-mount method,[12] cleared in anise oil, and fine dissected. At the fine dissection, the stroma was removed in such a way that the epithelium with the basal membrane and underlying tissue was as thin as possible. The entire epithelium piece was placed in a chamber filled with anise oil–colophonium and sealed with paraffin. The other half of the polyp was serial sectioned and stained with hematoxylin and eosin and PAS–alcian blue (Fig 1).

The goblet cells were counted in Reichart's projection microscope, x500, in counting fields of 0.01768 mm^2 distributed over the polyp half in the following way. From the stalk to the bottom, the polyp was divided by three horizontal lines: a proximal (near the stalk), a middle, and a distal line (Fig 2). Along these lines goblet cells were counted in each second counting field, going from left to right. In a similar fashion, the polyp was divided by vertical lines into left, middle, and right parts, and the goblet cells were counted from the stalk distally along the lines toward the bottom of the polyp. Areas lacking epithelium were passed over and are not included in the calculations.

In this way the goblet cell density could be determined on the entire surface of the polyp, and the

TABLE 2. GOBLET CELL DENSITY IN 14 POSTERIORLY SITUATED NASAL POLYPS

Pt No.	Goblet Cells per 0.01768-mm^2 Field												
	Horizontal Lines Median			Vertical Lines Median			All Countings				Counted Fields		
	Proximal	Middle	Distal	Left	Middle	Right	Median	Range	95% Confidence Limits	25th-75th Percentiles	Total No.	Fields Without Goblet Cells No.	Fields Without Goblet Cells %
15	56	4	2	0	5	75	5	0-186	3- 10	0- 10	158	41	26
16	7	—	16	—	—	—	7	1- 41	1- 19	3- 14	11	0	0
14	161	182	127	114	168	227	168	37-244	141-182	124-192	55	0	0
7	44	88	50	56	76	51	63	0-300	51- 82	41-118	112	6	5
17	171	28	13	68	52	3	46	0-219	19- 66	6-138	109	18	17
10	66	83	36	6	13	33	43	0-179	33- 71	4-107	85	12	14
18	138	152	82	—	76	141	138	18-188	59-152	46-153	40	0	0
18	107	147	145	0	129	116	129	0-190	102-145	76-154	59	10	17
13	63	116	32	24	97	78	79	0-152	63- 95	34-109	66	12	19
19	181	218	169	162	135	36	169	0-239	149-186	130-204	68	3	4
20	171	85	54	172	131	22	92	0-231	72-118	41-152	117	12	10
21	127	143	86	128	119	138	122	3-202	113-132	94-152	123	0	0
21	174	—	109	186	182	178	178	83-241	163-189	156-199	43	0	0
22	52	77	117	74	175	147	136	0-250	96-167	51-202	95	7	8
Interindividual median	117	102	68	91	119	78	107	5-178	7-168	46-138	77	7	7

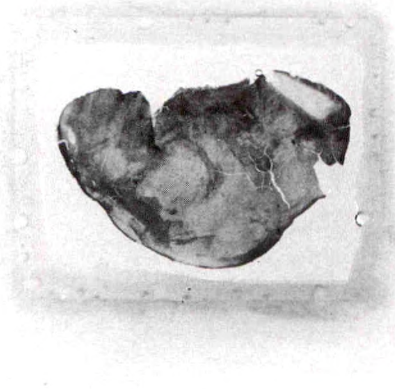

Fig 1. Stained surface of whole-mount prepared polyp half.

median density was calculated along the six lines. Similarly, the median density for the entire polyp, including areas close to the stalk and distal segments of the polyp, was determined.

RESULTS

The study of the goblet cell density in whole-mount specimens revealed three conspicuous findings: 1) the distribution is extremely irregular, and there are areas completely lacking goblet cells; 2) the density is very low compared with other parts of the respiratory airways — this applied to anterior as well as posterior polyps; 3) there are large differences in the median density among individual polyps; and 4) no general regularity in the distribution of goblet cells could be demonstrated in the nasal polyps.

Distribution and Density. The individual goblet cells appeared in the whole-mount specimens as round to oval blue patches on a pale blue background, resembling those found in the nose and sinuses (Fig 3). The very irregular distribution of goblet cells is due to the fact that certain areas of the polyps completely lacked goblet cells, whereas others showed a relatively high density. The quantitative data on the irregular distribution and the small median density appear in Tables 1 and 2. In some polyps with a very small median density, the upper range limit could be high. Range, 25th-75th percentiles, and 95% confidence limits showed relatively high values in all polyps, and in several polyps there were counting fields without goblet cells.

Anterior and Posterior Polyps. The interindividual median density of goblet cells of all 15 anterior polyps was 61 cells, as determined in counting fields of 0.01768 mm^2 (Table 1), corresponding to 3,450 cells/mm^2. The interindividual median density of the 14 polyps located behind the anterior polyp was 108 cells per field (Table 2), corresponding to 6,050 cells/mm^2. This apparently large difference in median density was, however, not statistically significant (Mann-Whitney test, $p > .05$). This finding was confirmed by the 95% confidence limits of the interindividual median density, which were 23 to 92 cells per field for the anterior polyps and seven to 168 cells per field for the posterior polyps. The lower interindividual range limit was even lower in the group of posterior polyps (Table 2). Polyps with an extremely low median density were thus found

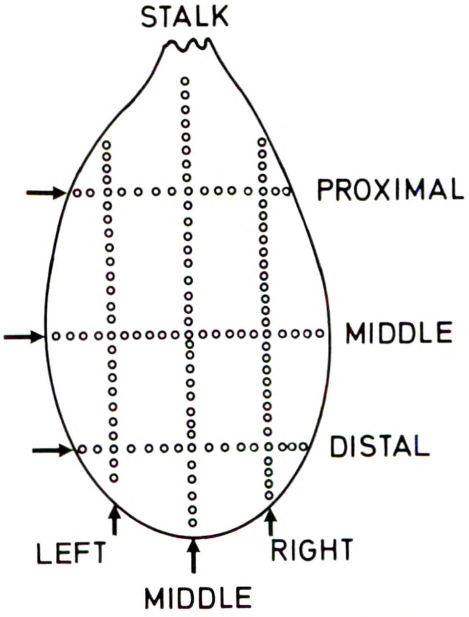

Fig 2. Schematic illustration of polyp half, showing lines drawn to create fields for counting goblet cells.

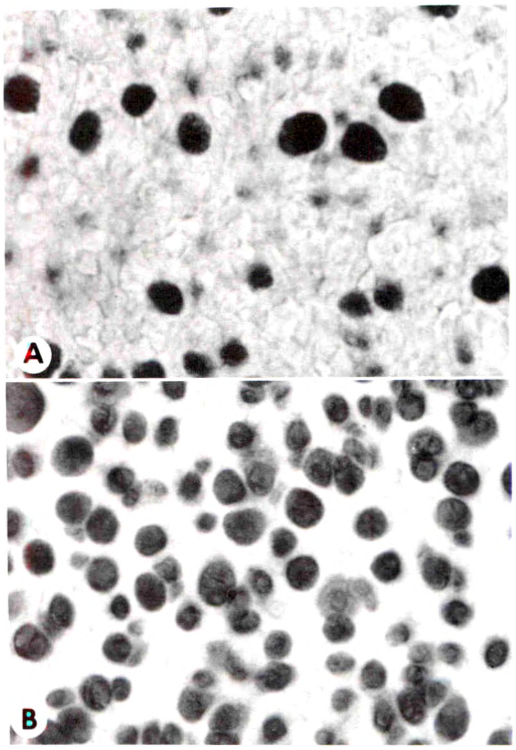

Fig 3. Goblet cells in whole-mount stained mucosa (original x500). A) Low density, irregular distribution. B) High density.

TABLE 3. GOBLET CELL DENSITY PROXIMAL TO STALK, IN MIDDLE PART, AND IN DISTAL PART OF ANTERIOR AND POSTERIOR POLYPS

	Anterior Polyps			*Posterior Polyps*			*All Polyps*		
Location	*Median*	*95 % Confidence Limits*	*Range*	*Median*	*95 % Confidence Limits*	*Range*	*Median*	*95 % Confidence Limits*	*Range*
Proximal part	34*	3- 78	0-184	117*	44-171	7-181	65	32-107	0-181
Middle part	85	25-106	7-126	102	28-152	4-218	94	46-116	4-218
Distal part	76	5-141	4-168	68	13-145	2-169	83	36-106	2-169

*Mann Whitney $p < .05$.

to be equally frequent among anterior and posterior polyps. Similarly, relatively high median densities can be found in anterior as well as posterior polyps.

We found no grounds for assuming that the density of goblet cells was uniform in the individual patient. In one case, anterior polyps from both sides of the nose were examined. The difference in median density was large (Table 1, patient 11). In four patients, both an anterior and a posterior polyp were examined, and in two patients, two posterior polyps were studied (Table 2, patients 18 and 21). Also, in these cases there was no tendency toward a uniform density. In some patients, the second polyp in the anteroposterior direction was examined, while in others the third or fourth polyp was studied. There was no tendency for posterior polyps to have the highest density of goblet cells.

Density in Different Locations. In anterior polyps, the interindividual median density of goblet cells was considerably lower in segments proximal to the stalk than in distal segments, although the difference was not statistically significant (Table 3). In posterior polyps, the reverse was found, with a higher density close to the stalk and the lowest density in distal parts. Also here, however, the difference was not statistically significant. The only significant difference found was a lower median density in the areas close to the stalk of the most anterior polyp compared with that found in the posterior polyp (Mann-Whitney test, $p < .05$).

Analysis of differences in interindividual median density along the vertical lines showed no statistically significant differences between left, middle, and right parts, in either anterior or posterior polyps (Table 4).

Epithelial Types and Goblet Cell Density. The histologic examination of serial sections of polyps showed several epithelial types, such as pseudostratified ciliated epithelium (Fig 4A), cylindric epithelium, cuboid epithelium, transitional epithelium (Fig 4B), and stratified epithelium (Fig 4C). Also, the thickness of the epithelial types varied.

The predominant type of epithelium was pseudostratified, cylindric, and ciliated, displaying the highest density of goblet cells, although this varied greatly within the same type of epithelium and within the same polyp. Even in polyps completely lined with pseudostratified cylindric epithelium, the density varied. The height of the pseudostratified cylindric epithelium appeared to have some influence on the density of goblet cells: a high epithelium with pronounced basal cell hyperplasia showed the highest density, whereas in lower pseudostratified epithelium the density was generally lower. However, there were several deviations from this rule, too.

One-, two-, or three-layered stratified cuboid epithelium was found sporadically, displaying a relatively low goblet cell density.

Transitional epithelium appearing with cylindric cells basally and round cells superficially, which is of the same structure as in the bladder, was encountered in quite a few places. In areas with a high transitional epithelium, the goblet cell density was higher than in areas with a low transitional epithelium. (In high transitional epithelium the superficial stratification is higher than in low transitional epithelium.) Stratified unkeratinized squamous epithelium with a low goblet cell density was rarely found. Both the transitional and the squamous epithelium contained areas completely devoid of goblet cells; this applied to anterior as well as posterior polyps. Both types of epithelium were found on posterior polyps, too.

DISCUSSION

Many factors may conceivably affect the goblet cell density of the polyps. These include 1) the air-

TABLE 4. GOBLET CELL DENSITY OF LEFT SIDE, MIDDLE, AND RIGHT SIDE OF ANTERIOR AND POSTERIOR POLYPS

	Anterior Polyps			*Posterior Polyps*			*All Polyps*		
Location	*Median*	*95 % Confidence Limits*	*Range*	*Median*	*95 % Confidence Limits*	*Range*	*Median*	*95 % Confidence Limits*	*Range*
Left side	40	23- 78	7-166	91	0-162	0-186	56	24-114	0-186
Middle	66	3-127	0-202	119	13-168	5-182	96	35-129	0-202
Right side	43	17-113	8-144	78	22-147	3-227	53	30-116	3-227

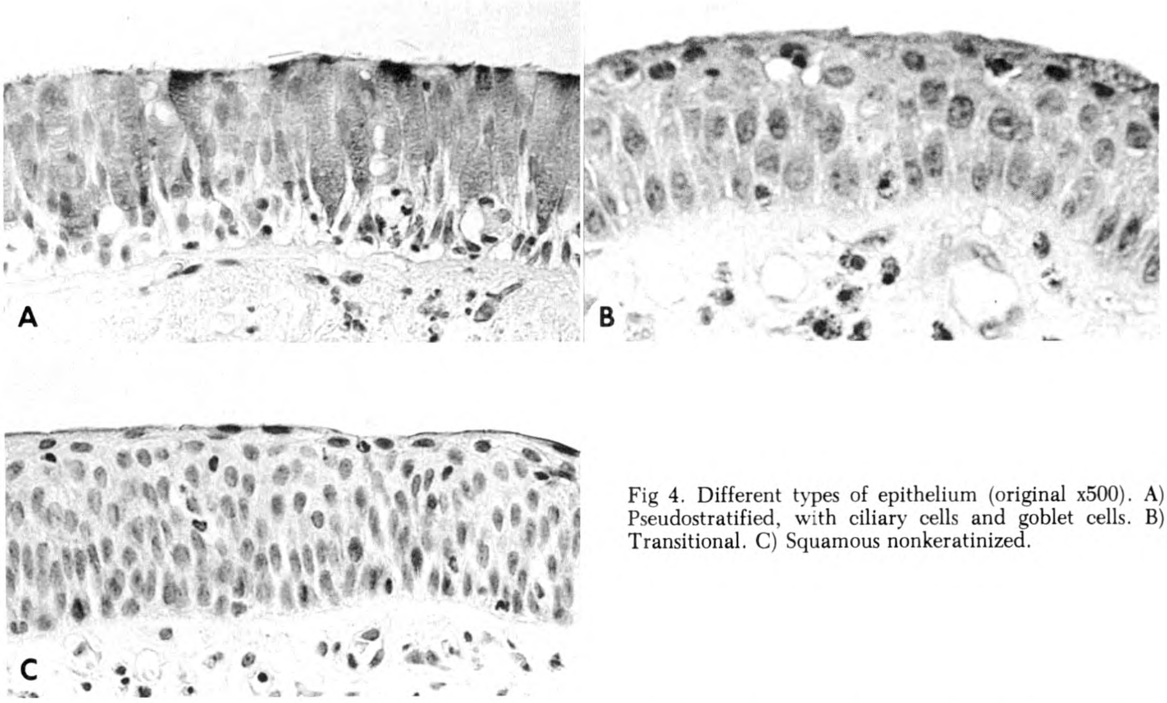

Fig 4. Different types of epithelium (original x500). A) Pseudostratified, with ciliary cells and goblet cells. B) Transitional. C) Squamous nonkeratinized.

flow, 2) contact between surfaces of individual polyps, 3) infection, 4) allergy, 5) growth rate of the polyp, 6) age of the polyp, 7) traumatic damage of the epithelium and its regeneration rate, and 8) different epithelial types and their thickness.

Airflow. The influence from the airflow may account for the fact that a smaller median density of goblet cells is found in the anterior polyps compared with the posterior ones and that certain differences are found between distal and proximal parts of the polyp. In experimental closure of one nostril in rabbits, we found a low goblet cell density on the open side and an increased density on the closed side.[13] The high median density at a level with the stalk of the posterior polyp may be attributed to the lack of airflow in this part of the nose, in which the ceiling is packed with swollen mucosa and polyps. The low density found distally on the posterior polyps also may be affected by the airflow; this part of the polyp is often visible in the nose and is presumably exposed to the airflow .

On removal of the polyps, the anterior polyp was kept apart from the others and the surface of the wound near the stalk could be clearly identified proximally. It could not be determined how much of the part of the polyp near the stalk had been left behind and how the individual polyp had been situated in the nose. On anterior rhinoscopy the anterior surface — or the anterior edge — is often visible, and the influence of the airflow might conceivably be greatest on these particular segments, which presumably vary in size from polyp to polyp. Areas close to the septum may be visible in a few cases, whereas the lateral and posterior areas are not visible and therefore not greatly exposed to the airflow. Being unable after the removal of the polyps to reconstruct the exact location of the individual polyp, we must accept some uncertainty regarding the influence of the airflow on both epithelial changes and goblet cell density. Another study design ensuring that exposed parts of the polyp are marked before removal would increase our knowledge of the impact of the airflow.

Contact Between Surfaces. Theoretically, the mechanical contact between polyp surfaces may give rise to an irritation resulting in an increased goblet cell density. Histologically, however, there is no indication that some areas of the polyp have an increased vessel dilatation and cell infiltration, just as there are no areas with a particularly high density in association with subepithelial cell infiltration or vessel dilatation.

Infection and Allergy. Both infection and allergy have been claimed to be the cause of polyps.[14] An increased goblet cell density in the nasal mucosa has been described in nasal infections[15] and in nasal allergy.[16,17] However, quantitative analysis using the whole-mount method indicated a lower than normal goblet cell density in a patient with allergy.[18] Polyps from patients with clinical signs of allergy did not show a higher density than was found in patients without allergy.

Growth and Age. The genesis and place of origin of the nasal polyps have given rise to many hypotheses. The polyps have been claimed to originate in the ethmoid and be transferred to the nose by necrosis of the bone septa.[4] Other researchers found that the polyps arise in the nasal mucosa that bulges out because of the formation of exudate either between the bone and the mucosa[1] or in the subepithelial layer of the mucosa.[19] Our studies of the mucous glands of the nasal polyp[20] made us propose the theory[21] that edema and infiltration of the mucosa make the epithelium burst, permitting granulation tissue to protrude and become epithelialized. We found indications that the epithelium of small polyps was more immature and the stroma looser than in larger and older polyps.[21] In the present material, we could relate directly the age of the polyps to the goblet cell density. However, further studies are warranted to elucidate these interesting aspects and to increase our understanding of the regeneration ability and turnover of the respiratory epithelium.

Damage and Regeneration. Lately, various degrees of epithelial changes have been attributed to allergic reactions and considered to be at least partly responsible for rhinorrhea in allergic rhinitis.[22] We have previously, and also in the present study, observed epithelial defects that we consider to be artifacts. If these epithelial defects were caused by the disease, a local reaction of the stroma would be present at the site of damage. Furthermore, signs of regeneration in the form of an epithelium with a lower goblet cell density would be present. We did observe one- and two-layered epithelium in addition to stratified cuboid epithelium, but not to any great extent, and not in association with epithelial defects. These issues,[22] however, deserve further clarification by systematic studies, which the whole-mount method gives us the possibility to do.

Epithelial Type and Thickness. As stated, some correlation was found between the epithelial type and the goblet cell density, the latter being high in pseudostratified cylindric epithelium and low in cuboid stratified epithelium. However, great variations were demonstrated within the individual epithelial types, possibly relating to the stage of turnover of the epithelium, the degree of basal cell hyperplasia, and other as yet unknown factors.

Presumably, all of the mentioned factors exert an influence on the goblet cell density, and combinations of factors further complicate matters. There is apparently no simple explanation of the variations in goblet cell density, and the present study leaves several unanswered questions that can and should be elucidated further by systematic studies. Nasal polyps represent a very interesting source of human, easily available respiratory epithelium that with improvement of the dissection technique might form the basis of experimental studies of the epithelium.

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HISTOPATHOLOGIC STUDY OF THE PERILYMPH-SUCTIONED LABYRINTH

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A small amount of perilymph was suctioned from the scala tympani through the round window membrane of guinea pigs. The animals either were killed immediately after the suctioning or were kept alive for 1 to 3 months. For morphologic study, the conventional celloidin embedding method was employed, and the temporal bones were serially sectioned. Various kinds and degrees of changes in the membranous labyrinth were observed: hydrops, collapse, and rupture. Loss of outer hair cells in the upper turns of the cochlea was noted in the 1- to 3-month recovery specimens. These findings are identical to those found in animals in which artificial perilymph was injected into the subarachnoid space in order to produce experimental perilymphatic fistula. After comparing morphologic changes of the membranous labyrinth following use of each method, we concluded that perilymph suctioning from the round window can be used as an animal model of perilymphatic fistula.

KEY WORDS — animal model, perilymph suctioning, perilymphatic fistula.

INTRODUCTION

The cause of perilymphatic fistula has not yet been elucidated. Since simple perforation of the round window membrane cannot cause severe hearing loss,[1,2] pathologic changes within the labyrinth were postulated as the cause of hearing loss in patients with perilymphatic fistula. Following the concept of an explosive mechanism of perilymphatic fistula,[3] we injected artificial perilymph into the subarachnoid space in order to produce rupture of the round window membrane. This was observed to occur by direct microscopic visualization of the membrane. These experiments revealed that the membranous labyrinth collapsed, ruptured, or bulged, with round window membrane rupture in the specimens observed immediately or 1 to 3 months after the injection.[4] In "chronic" specimens, loss of outer hair cells was observed in addition to the pathologic changes in the membranous labyrinth.

We thought that suctioning of perilymph through the round window membrane might produce changes in the membranous labyrinth similar to those observed in the injection animals.

The purpose of the present paper is to describe the histopathologic changes in the guinea pig inner ear from which perilymph was suctioned, and to compare the damage to the labyrinth with that of injection-induced changes, which were produced by injecting artificial perilymph into the subarachnoid space.

MATERIAL AND METHODS

Thirty-seven healthy Hartley guinea pigs weighing 250 to 300 g were used in this series of experiments. Intraperitoneal Nembutal anesthesia (40 mg/kg) was employed. After a skin incision was made posterior to the pinna, a small hole was opened in the right tympanic bulla.

Four microliters of perilymph was suctioned from the cochlea through the right round window membrane. The fluid was removed within 1 second by use of a micropipette (Pipetteman P-20 Gilson) connected to a 27-gauge needle. After the suctioning of perilymph, the round window membrane was left unsealed. Twenty-two animals, termed acute, were fixed by intravital perfusion of Heidenhain-Susa solution immediately after the suctioning. This procedure took about 15 minutes. Nine animals, termed chronic, were kept alive for 1 to 3 months before they were perfused with fixatives and specimens of the inner ear were processed for microscopic observation. Histologic sections were prepared by the technique described in our previous publication.[4] The labyrinths of one animal were removed, prefixed in 0.1 mol/L cacodylate buffer with 2.5% glutaraldehyde, postfixed in a 2% solution of osmium tetroxide, and examined with a transmission electron microscope.

In five control animals, a perforation was made in the right round window membrane with a 27-gauge needle. The temporal bones of two animals were processed for microscopic study immediately

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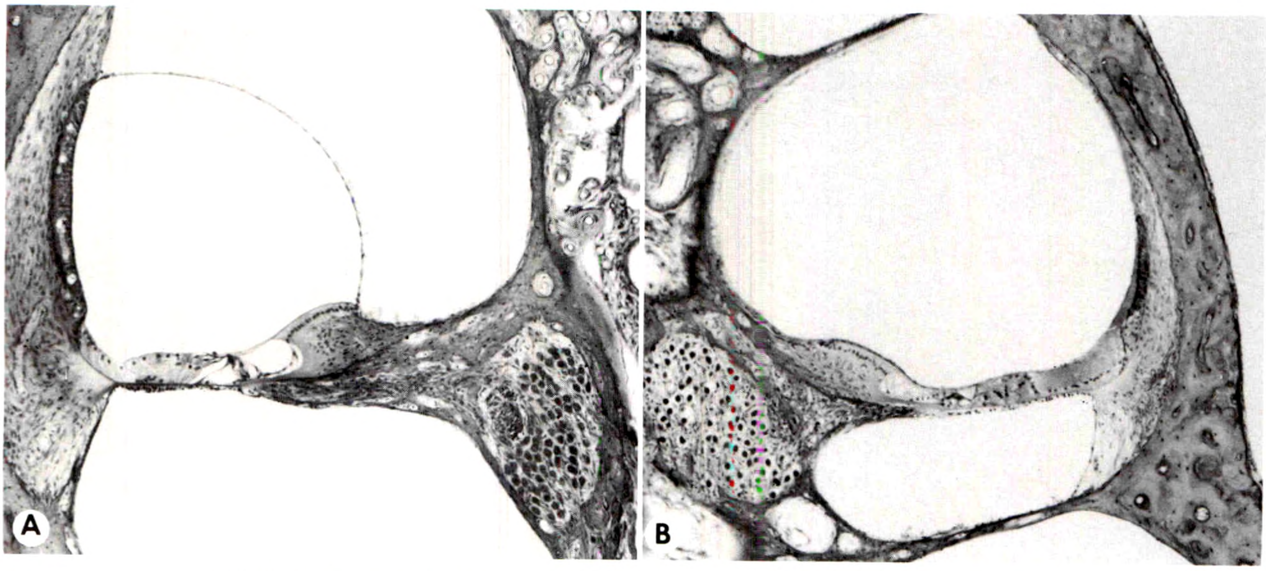

Fig 1. Acute specimen observations. A) Hydrops. B) Collapse of Reissner's membrane.

after surgery; three animals were kept alive for a month before processing.

RESULTS

Acute Specimen Observations. The findings in the "acute" specimens are based on the results in 22 guinea pigs. Precipitate was found in the fluid spaces of the inner ear. One animal showed subluxation of the right stapes. The cochlea and vestibular apparatus were normal in this animal.

The membranous cochlea showed various changes. For Reissner's membrane, 13 of 22 ears showed no change, 2 had hydrops, and 7 were collapsed. In the hydropic ears, Reissner's membrane bulged moderately in all turns of the cochlea (Fig 1A), but in none of the animals was the bulging so marked as to occupy the whole scala vestibuli. Collapse of Reissner's membrane was caused by its rupture. The ruptured membrane completely covered the organ of Corti, which was also collapsed in that area (Fig 1B). Aside from the region of the rupture, Reissner's membrane showed mild collapse.

In the animals with hydrops, nearly all the outer hair cells were intact, except for one ear in which there was marked compression of the organ of Corti in the upper turns. There was an indentation in the reticular lamina between the first and the second row of the outer hair cells. The tectorial membrane also showed a bending at the indentation. The spiral ganglion cells showed no morphologic changes. The tympanic lamella did not show any changes.

Morphologic changes in the membranous labyrinth of the vestibular apparatus were also variable, as shown in Table 1.[4] The pars superior did not show hydrops, even in the presence of hydrops in the cochlea. Collapse of the pars superior occurred together with that of the pars inferior. However, in some animals, collapse of the membranous labyrinth occurred only in the cochlea. The most common finding was collapse of the ampullae of the semicircular canals, which was particularly severe in the posterior ampulla. The ampullary wall was so severely collapsed that it touched the crista ampullaris. A minor change observed in the semicircular canals was separation of the two layers of the membranous labyrinth (Fig 2).

The pars inferior did not show consistent uniform changes. Two cochleas showed endolymphatic hydrops in the cochlea, whereas none of them showed hydrops in the saccule. Two ears demonstrated compression of the organ of Corti in the upper turn (Fig 3). Four inner ears showed collapse of the

TABLE 1. ACUTE CHANGES IN MEMBRANOUS LABYRINTH

		No. of Ears	
Cochlea	*Vestibular Apparatus*	*Suction Animals*	*Injection Animals**
Normal	Normal	8	10
	Semicircular canals collapsed	4	9
	Semicircular canals collapsed, saccular hydrops	0	2
	Semicircular canals, saccule, utricle collapsed	1	1
Hydrops	Normal	1	5
	Semicircular canals collapsed	0	3
	Semicircular canals, utricle collapsed	1	0
	Saccular hydrops	0	1
Collapsed	Collapsed	4	4
	Normal	1	2
	Saccule collapsed	1	0
	Saccule, utricle collapsed	1	1
Total		22	38

*Artificial perilymph was injected into subarachnoid space. Data from Nomura and Hara.[4]

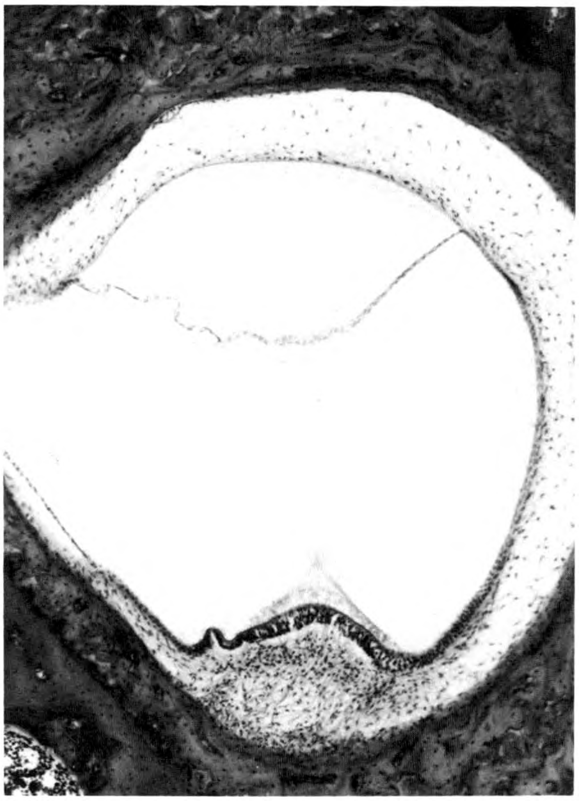

Fig 2. Acute specimen observations. Separation of two layers of membranous labyrinth of posterior ampulla.

whole membranous labyrinth. No remarkable morphologic changes were observed in the endolymphatic sac in any of the animals.

Chronic Specimen Observations. Chronic changes were observed in nine guinea pigs. The fluid spaces were clear in all animals. None of the ears revealed hydrops in the cochlea. In two of nine ears, the outer hair cells were missing in the upper turns of the cochlea (Fig 4). The population of the spiral ganglion cells appeared normal.

One animal was perfused with fixatives for electron microscopic observation 17 days after the suctioning. An outer pillar cell demonstrated a strong bending into the tunnel of Corti. Cytoplasm in both the inner and outer pillar cells was swollen. These changes decreased the size of the tunnel of Corti (Fig 5). The three rows of outer hair cells were damaged or missing. Marked swelling of the cytoplasm was seen in Deiters' cells.

Most of the specimens in which the cochlear duct was collapsed were found to show collapse of the whole vestibular apparatus. The findings in the membranous labyrinth are summarized in Table 2.[4,5] Changes in the organ of Corti are shown in Table 3.[4,5]

Our observations show that suctioning of perilymph through the round window membrane can produce pathologic changes in the labyrinth similar to those produced by the injection of artificial perilymph into the subarachnoid space. None of the control animals showed any pathologic changes.

DISCUSSION

Perilymphatic fistula occurs in ear trauma, congenital malformation of the inner ear, and ear surgery. In idiopathic perilymphatic fistula, the fistula has no apparent cause. Goodhill[3,6] postulated that increased CSF pressure or middle ear pressure is one of the causes of perilymphatic fistula. Simmons[7] proposed double membrane rupture as a cause of acute sensorineural hearing loss. However, the paucity of histopathologic studies of human temporal bones[8-10] makes it difficult to explain the clinical symptoms pathophysiologically. Therefore, animal experiments are essential for elucidating the nature of perilymphatic fistula.

Our previous study[4] confirmed that the injection of artificial perilymph in the subarachnoid space produces pathologic changes in the membranous labyrinth and the sensory cells.

In the present experiment, the pars inferior did not show uniform changes. Two cochleas showed endolymphatic hydrops. However, the saccule in

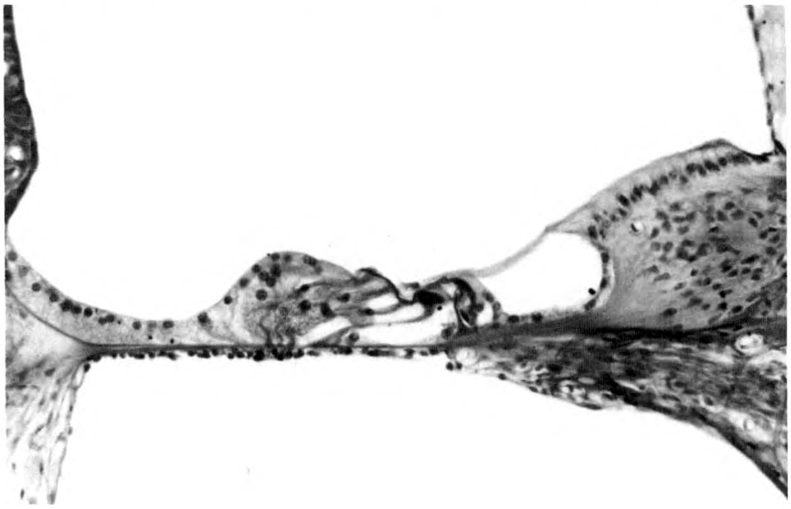

Fig 3. Acute specimen observations. Marked compression of organ of Corti.

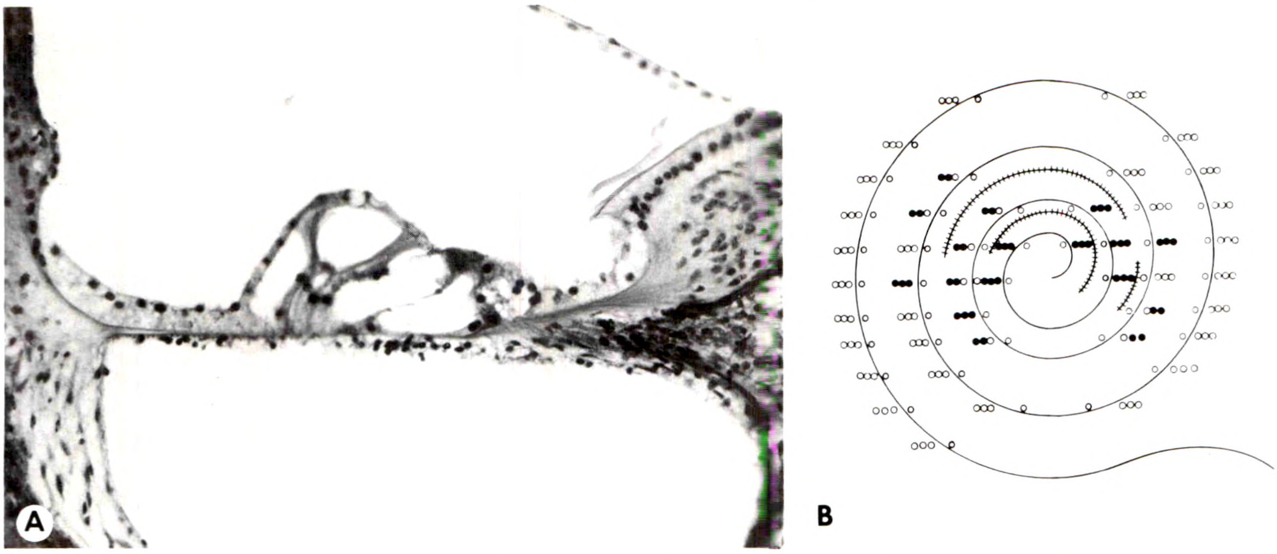

Fig 4. Chronic specimen observations. A) Loss of outer hair cells. B) Cytocochleogram of right ear (3 months after suction) showing hair cells (open circles), hair cell loss (closed circles), and strial atrophy (hatched line).

these animals did not show hydrops. These findings indicate that hydrops produced by perilymph suctioning is different from that produced by blockage of the endolymphatic duct and sac.[11]

A question may arise as to whether or not perforation of the round window membrane produces inner ear damage. This is not likely, on the basis of the lack of pathologic changes in our controls.

Endolymphatic hydrops was observed only in the acute specimens in which perilymph was suctioned. Thus, moderate hydrops in the suction animals seems to be reversible. This finding is quite similar to the results of acute injection-induced changes. Chronic observation of injection-induced changes revealed hydrops in only one animal, in which marked hydrops was produced by obstruction of the longitudinal flow of endolymph at the ductus reuniens and saccule.[5] However, the rate of hydrops formation was not similar in the injection and suction animals. This is due to minor changes in the experimental procedures and to differences in individual animals.

In contrast, collapse of the membranous labyrinth seems irreversible in the suction animals, as in the injection animals. This is obvious in comparing the rate of collapse in chronic suction animals (44%) with that in acute suction animals (32%).

The outer hair cells were missing in the suction animals that were kept alive for 3 months. The cytocochleograms in these animals were similar to

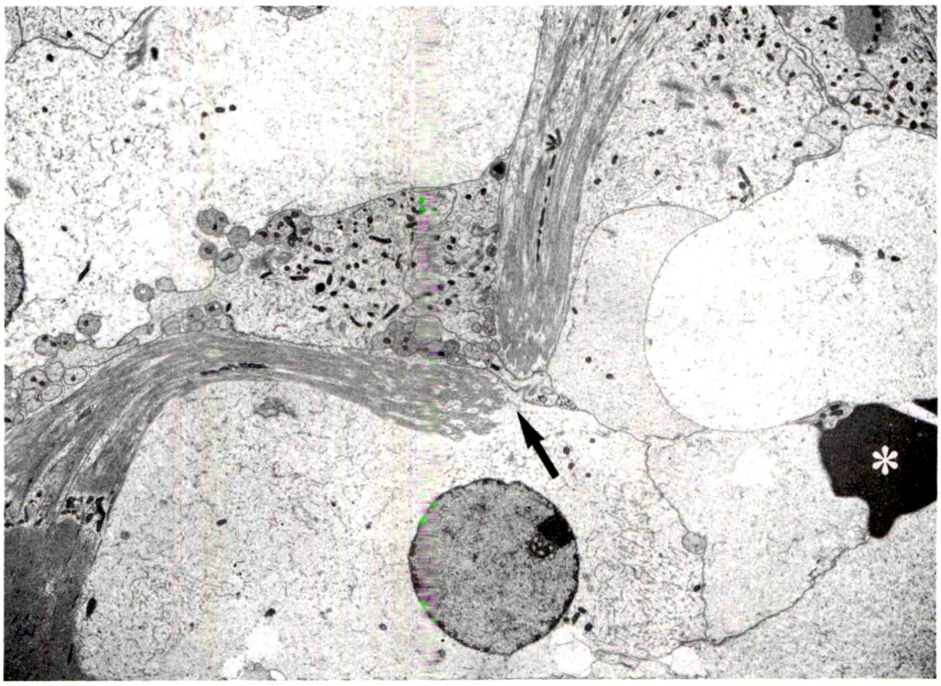

Fig 5. Chronic specimen observations. Strong bending of outer pillar cell (arrow) and extremely narrow space in tunnel of Corti (asterisk) (original x4,200).

TABLE 2. CHRONIC CHANGES IN MEMBRANOUS LABYRINTH

		No. of Ears	
Cochlea	*Vestibular Apparatus*	*Suction Animals*	*Injection Animals**
Normal	Normal	3	10
	Collapsed	1	5
	Saccular hydrops	1	2
Collapsed	Normal	1	0
	Collapsed	3	4
Hydrops	Collapsed	0	1
Total		9	22

*Artificial perilymph was injected into subarachnoid space. Data from Nomura and Hara[4] and Nomura et al.[5]

those for injection animals. The rate of hair cell loss in chronic injection animals (27%) was similar to that in chronic suction animals (22%).

An indentation of the reticular lamina between the first and second rows of the outer hair cells was seen in both injection and suction animals. The rate of compression in chronic injection animals (9%) was similar to that in chronic suction animals (11%). According to Fernández,[12] compression of the organ of Corti is not a postmortem artifact if fixation of the surrounding structures is done well. It is apparent from the present transmission electron microscopic study that the microtubules in the outer pillar cells are disrupted.

TABLE 3. CHANGES IN ORGAN OF CORTI

	Hair Cell Loss		Compression	
	Suction Animals	*Injection Animals**	*Suction Animals*	*Injection Animals**
Acute	0/22	0/38	2/22	2/38
Chronic	2/9	6/22	1/9	2/22

*Artificial perilymph was injected into subarachnoid space. Data from Nomura and Hara[4] and Nomura et al.[5]

In both groups, the collapse of the posterior ampulla was marked. The medial side of the ampullary wall was compressed toward the crista ampullaris.

The rates of collapse of the vestibular apparatus in acute and chronic suction animals (55% and 44%, respectively) were close to those in acute and chronic injection animals (53% and 45%, respectively).

The animals in the perilymph suction group did not show long-lasting nystagmus, but did show head tilt toward the operated side.

In summary, changes produced in the labyrinth by suctioning are essentially similar to those produced by perilymph injection. As the suctioning procedure is simple, it can be used as a method of producing an animal model of perilymphatic fistula. The suctioning of perilymph through the round window membrane may produce drastic changes in the membranous labyrinth.

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IMAGING CASE STUDY OF THE MONTH

MAXILLARY SINUS MUCOCELE

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The following presentation exemplifies our cases of maxillary sinus opacity. This finding on radiography requires use of more specific imaging studies such as computed tomography (CT) or magnetic resonance imaging for specific diagnosis.

CLINICAL FINDINGS

The patient was a 76-year-old woman who found that her partial denture no longer fit well along the right maxillary alveolar ridge. Since she was out of state on vacation, she sought evaluation from an oral surgeon recommended by a friend.

Examination revealed swollen red mucosa overlying a tender soft tissue mass in the right gingival surface of the maxilla. Antibiotics and hot applications over the area produced slight reduction in the swelling. A Waters view showed right maxillary sinus opacity (Fig 1).

Suspecting an abscess, the oral surgeon obtained a CT examination of the sinuses and maxillary alveolus. The patient returned home for further care.

RADIOGRAPHIC FINDINGS

The Waters view shows complete right maxillary sinus opacity. This and other conventional views suggested thinning of the lateral maxillary sinus wall.

Both axial and coronal CT views were obtained. A midmaxillary axial CT showed marked expansion of the right maxillary sinus with a bulging nasal surface and thinned anterior surface (Fig 2A). The main density of the expansile sinus mass is much less than that of muscle and consistent with fluid. A lower cut through the alveolar border showed thinning posteriorly on the right with an overlying soft tissue mass as demonstrated by Fig 2B.

An oblique coronal view is shown in Fig 3. In this examination, the alveolar surface of the maxilla is extensively destroyed. Superiorly, the orbital surface of the maxilla is markedly thinned. Thinning of the nasal surface of the maxilla is also present and bulges into the nasal fossa. The changes were thought most consistent with a maxillary sinus mucocele that had expanded and thinned the sinus walls.

SURGICAL AND PATHOLOGIC FINDINGS

Further historical review revealed that the patient had a Caldwell-Luc procedure 15 years before the onset of her present complaint.

It was elected, since the maxillary walls were so thinned, to approach the mass through the nose. A large medial maxillary wall incision was made, and a cyst was found. Local tissue and several biopsies of the cyst wall demonstrated thick fibrous tissue surrounding the epithelial wall of the cyst. Because of the marked thinning present, creation of the large nasoantral window, about 4 cm in diameter, was considered adequate therapy.

DISCUSSION

Symptomatically, the maxillary alveolar mass was considered to be a neoplasm or an abscess. The expansile change of the maxillary sinus walls and

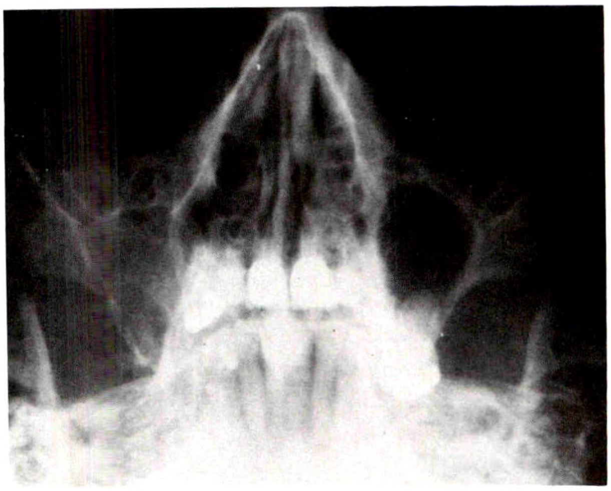

Fig 1. Waters view with opaque right maxillary sinus and poorly defined walls.

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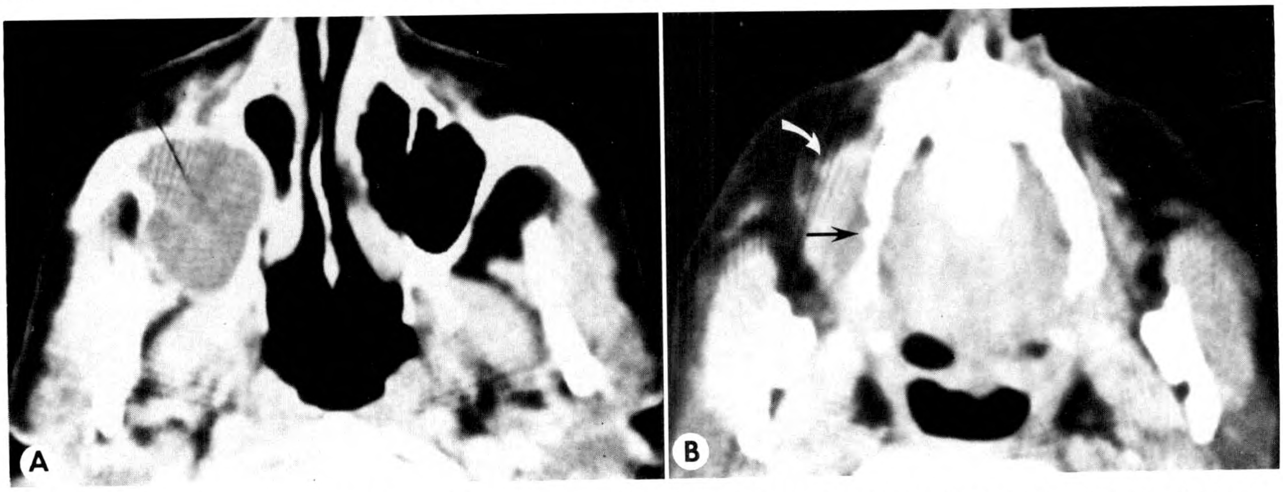

Fig 2. Axial computed tomographic views. A) Midmaxillary view with expansile thinning of anterior, lateral, and nasal surface on right side by low-density cyst. B) Alveolar view with thinning and erosion of posterior alveolus (black arrow) and overlying soft tissue thickening (white arrow).

low density of the cyst content as seen on CT were most consistent with a mucocele.

Maxillary sinus mucoceles have a variable prevalence. In Norway, Natvig and Larsen[1] found an incidence of three maxillary mucoceles among the 112 mucoceles they studied. Som and Shugar[2] found maxillary sinus mucoceles in 8 of 79 patients whom they studied, giving a 10% prevalence.

Large series of mucoceles have been reported in the Japanese literature. Kaneshiro et al[3] reported their findings in 71 cases. Hasegawa et al[4] reported on 132 cases of maxillary mucocele. All of the Japanese cases followed maxillary sinus operations.[3,4] Zizmor et al[5] reported that half of their 22 cases resulted from sinus operations.

Som and Shugar[2] noted that the most common cause of mucoceles is the presence of chronic infections or allergic disease that closes the sinus ostium. Surgery is their second most common cause. Fractures may close the sinus ostium or entrap mucosa along the fracture line, but this occurs infrequently. A neoplasm may obstruct a sinus ostium and produce a mucocele. Som and Shugar[2] are the only authors who illustrate such a patient. In their case a nasal carcinoma obstructed the maxillary ostium.

In the series of Kaneshiro et al,[3] the maxillary mucoceles appeared most commonly between 10 and 24 years postoperatively. The shortest time period was 7 years, and the longest, 40 years, for mucocele production.

Som and Shugar[2] have described the CT findings in mucoceles of the maxillary sinus. These lesions produce diffuse opacity with thinning of the walls of the sinus. This change must be differentiated from similar expansile changes produced by an ossifying fibroma. This lesion occurs at a much earlier age than maxillary mucoceles.

If sinus wall thinning has progressed to erosion of the sinus wall or walls, the erosion must be differentiated from a sinus malignant neoplasm.

In summary, our patient presented with symptoms suggesting a maxillary alveolus infection or neoplasm. The CT examination more strongly indicated a mucocele that developed 15 years after a surgical procedure.

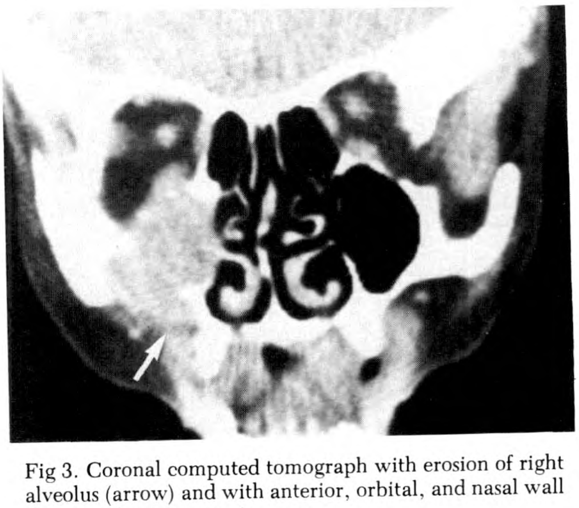

Fig 3. Coronal computed tomograph with erosion of right alveolus (arrow) and with anterior, orbital, and nasal wall thinning due to expansion.

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PATHOLOGY CONSULTATION

BIOPSY OF THE LIP AND SJÖGREN'S SYNDROME

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The degree of focal chronic sialadenitis in a labial salivary gland biopsy specimen, expressed in terms of a semiquantitative focus score, is the best contemporary assessment of the salivary component in Sjögren's syndrome. A labial salivary gland focus score of >1 focus per 4 mm² serves as an acceptable threshold for the diagnosis.

A diagnosis of either primary or secondary Sjögren's syndrome always requires a confirmation of its salivary component.[1,2] None of the techniques used for evaluation of the salivary component — radiographic, biochemical, or histopathologic — can currently provide sufficiently specific information to allow its use as a sole criterion for diagnosis. Nonetheless, Daniels[1,2] has offered a careful and reasoned rationale for the diagnostic utility of a labial salivary gland biopsy in a patient with a presumed diagnosis of Sjögren's syndrome. He has affirmed that focal, chronic sialadenitis in labial salivary glands is the single best predictor of the salivary component of the syndrome in terms of disease specificity, convenience, availability, and low risk.[2]

The diffuse exocrinopathic character of Sjögren's syndrome is exploited in biopsy of minor salivary tissues, since they have been shown to reflect the more clinically prominent major salivary gland involvement.[3] Three minor salivary tissue sites have been used for biopsy: the lip,[4] palate,[5] and anterior nasal septum.[6] The lip is now established as the preferred site, not only because of greater experience, but also because the palate and nasal mucosa have not had a definition of the inflammatory changes expected with the normal aging process or as a result of local agents or trauma.

With any of the three general biopsy methods of procuring labial salivary tissues, a midline biopsy is to be avoided. There are fewer glands in the midline, and they may even be absent in the elderly.[1] A trephine or "punch" biopsy is also not recommended, because it usually does not provide enough glandular tissue for examination. Of the two scalpel-based biopsy methods, the one described by Daniels[1,2] is superior to the elliptic excision that includes all tissue above the orbicularis oris muscle. As with all biopsies, Daniels's technique should be performed only through *normal-appearing* lower labial mucosa between the midline and the commissure.[1,2] A single 1.5- to 2.0-cm horizontal incision that just penetrates the epithelium of an everted mucosa is followed by blunt dissection and removal of separate salivary glands released from their enveloping fascia. After removal of at least five glands, the mucosa is reapposed by sutures. The nonuniform involvement of glands requires examination of a number of them, and the separation of each, if they are processed correctly, allows histopathologic sections to be made through the center of each gland.

It is now known that during the physiologic aging process nearly all of the constituents of labial salivary gland tissues are subject to continual alterations.[7-10] Age-dependent changes are principally related to acini, fibrous tissue, and intralobular ducts. Acinar atrophy, dilatation of ducts, and a stromal preponderance increase with age, are commonly associated with inflammation, and affect women earlier than men. Longitudinal studies have also shown that a complete fibrous or fibro-fatty atrophy of salivary glands is not an end stage of a long-standing

FREQUENCY OF SELECTED AUTOANTIBODIES IN SJÖGREN'S SYNDROME

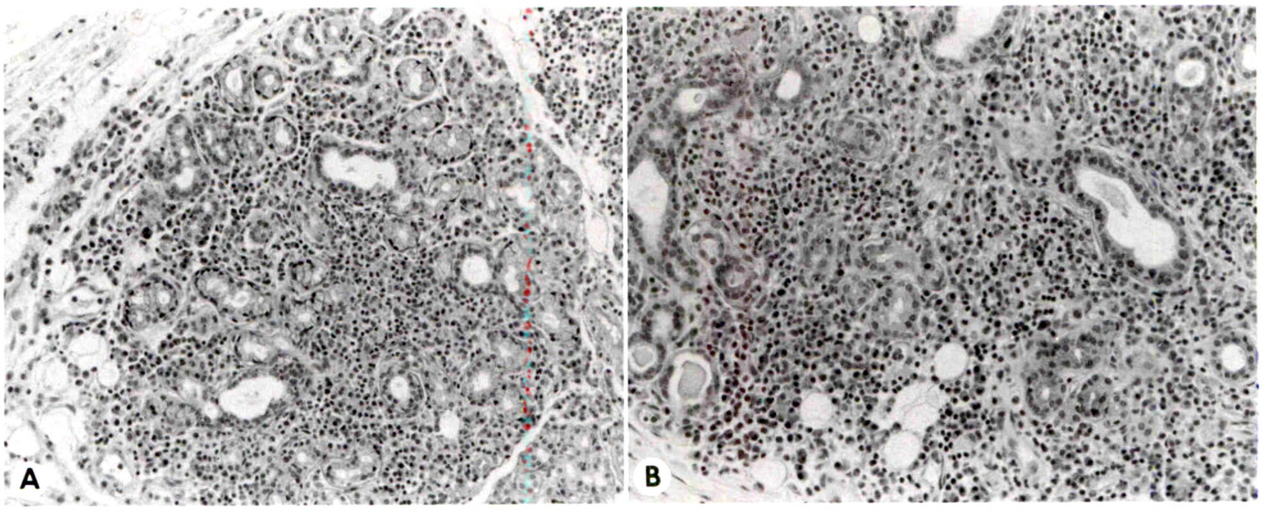
	Cases of Sjögren's Syndrome (%)	
Autoantibody	*Primary*	*Secondary*
Antinuclear (ANA)	60-90	Up to 100
Complement C3–fixing ANA	60-80	60-80
Anti SS-A, -B and/or -Ha	50-80	0-15 (RA) 60-90 (SLE)
Rheumatoid arthritis precipitin	5-15	70-90 (RA) 0-5 (SLE)
Anti-DNA	0	0 in active RA 95-100 in active SLE
Positive Coombs	0-15	5-20
Positive LE-cell phenomenon	0-20	20-40 (RA) 80-100 (SLE)
Salivary gland	30-60	10-40
Pancreatic duct cell	20-40	20-40 (RA)
Smooth muscle cell	20-40	20-40
Antimitochondrial	0-15	10-30
Liver cell membrane	5-25	20-40
Thyroid microsomal	10-20	10-20 (SLE)

Information from Manthorpe et al.[12]

RA — rheumatoid arthritis, SLE — systemic lupus erythematosus.

From the University of Texas M. D. Anderson Cancer Center, Houston, Texas.

REPRINTS — John G. Batsakis, MD, Dept of Pathology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.



Two labial salivary glands from same biopsy specimen from patient with Sjögren's syndrome. A) Showing characteristic focal lymphocytic and plasmacellular sialadenitis (H & E, original x80). B) Showing focal chronic sialadenitis (H & E, original x100). Biopsy focus score of >1 is strongly supportive evidence of Sjögren's syndrome.

Sjögren's syndrome.[1]

With all this in mind, four histopathologic descriptors are recommended for the examination of labial salivary gland biopsy specimens: 1) inflammation with acinar atrophy and fibrosis; 2) scattered to diffuse mild inflammation with little or no acinar atrophy; 3) features suggestive of a disease process other than those associated with Sjögren's syndrome, eg, sarcoid, other collagen diseases, lymphoma; and 4) *focal* lymphoid cell sialadenitis, defined as an inflammatory cell aggregate containing 50 or more lymphocytes, plasma cells, or macrophages. Germinal centers may be found in large foci.[1,2] A further characterization of the focal sialadenitis is required and is achieved by a focus score. The focus score is defined as the number of foci of inflammatory cells per 4-mm^2 gland section.[1,2]

Correlative studies[1,2] have consistently indicated that a labial salivary gland biopsy focus score of >1 focus per 4 mm^2 is an acceptable threshold for a diagnosis of the salivary component of Sjögren's syndrome. A focus score of 1 suggests the possibility of the syndrome, but specimens with scores <1 or nonfocal chronic inflammation should be considered as being either within normal limits or nondiagnostic.[1,2] It should also be noted that even in patients with Sjögren's syndrome, epimyoepithelial islands are not often found (approximately 2% of patients with the syndrome).[3]

To the semiquantitative and still-subjective focus score system, DeWilde et al[11] have added a morphometric method to better discriminate between patients with Sjögren's syndrome and control populations. They claim morphometry reduced the rate of false-positive diagnoses from 8.6% to 1.7% in their studies.

The many immunologic abnormalities demonstrated in patients with Sjögren's syndrome (see Table[12]) indicate altered functions of both B and T lymphocytes and a hyperactivity of the B lymphocyte. There is also evidence the B cell stimulation may be T lymphocyte–induced, since immunohistochemical staining of involved salivary glands shows a higher proportion of helper-inducer T cells relative to suppressor-cytotoxic T cells.[13] These findings provide little help in clinical diagnosis. For the present, the important salivary component of the syndrome is best defined by findings in the labial biopsy specimen (see Figure).

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DIZZINESS MANAGEMENT CONFERENCE

The Department of Otolaryngology and Audiology Services, Medical College of Ohio, will host a Dizziness Management Conference on June 9, 1990. For further information, contact Randa Mansour-Shousher, MS, CCC-A, Audiology, Medical College of Ohio, 3000 Arlington Avenue, Toledo, OH 43614; (419) 381-4012.

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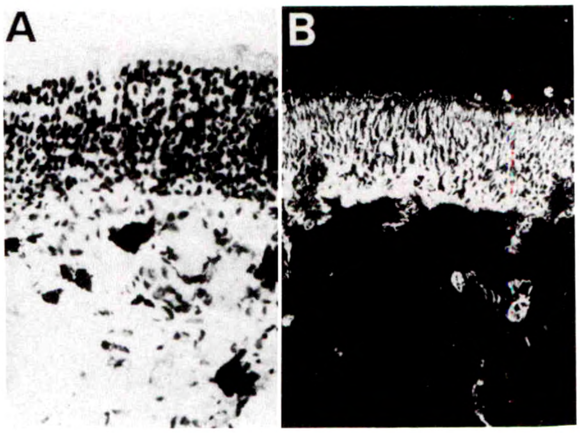
LETTERS TO THE EDITOR

To the Editor:

I refer to the article by Yamagishi et al (Immunohistochemical Analysis of the Olfactory Mucosa by Use of Antibodies to Brain Proteins and Cytokeratin, *Ann Otol Rhinol Laryngol* 1989;98: 384-8), which reports the results of immunohistochemical staining of the olfactory mucosa. Figure 5 in this article shows that cytokeratin (CK) immunoreactivity is present solely in the basal cells of the guinea pig's respiratory and olfactory epithelia. These findings are in apparent conflict with several previously published studies.

Positive staining of the respiratory epithelium with CK antiserum throughout its thickness is a well-known fact and needs no proof. Additionally, several studies have shown the presence of CK throughout the thickness of the olfactory epithelium, in humans[1] as well as in other vertebrates,[2-4] including staining of epithelial cells of Bowman's glands in the lamina propria (see Figure). Since the authors failed to provide details regarding the specificity of their antibodies, the results of their work, at least concerning anti-CK staining, should be viewed carefully.



Cryostat sections of bovine olfactory mucosa (original x250). A) Stained with hematoxylin and eosin. B) Immunofluorescently labeled with antibodies to cytokeratin. Cytokeratin immunoreactivity is present throughout all layers of olfactory neuroepithelium.

It is difficult to determine the source of this discrepancy. Yet, in the absence of details concerning the polypeptide specificity of the antibodies used by Yamagishi et al, one cannot exclude the possibility that their antibodies are uniquely reactive with a subgroup of CKs that are uniquely expressed in the basal cells. This observation is potentially interesting, providing the authors determine and report the exact polypeptide specificity of their antibodies.

The presence of CK, a characteristic epithelial intermediate-filament tissue marker, in a tissue composed of olfactory sensory neurons and glialike supporting cells is a unique feature and serves to confer mechanical resistance on the tissue exposed on the surface of the nasal cavity.

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To the Editor:

Cytokeratin (CK) is a cytoskeletal protein that is specific for epithelial components, and it has been used as a marker substance of epithelial cells. Recently it has been recognized that many subtypes of CK exist and their expression (immunoreactivity) is considerably different among cells. One of the purposes of our study was to identify and distinguish olfactory receptor cells, supporting cells, microvillar cells, and basal cells by use of immunocytochemical staining. For that reason, we chose an antiserum against CK that stained only basal cells, rather than CK antisera that immunolabeled all cellular elements of the olfactory epithelium. The CK antibody used in our study was a polyclonal anti-CK antiserum (DAKO) that was raised in a rabbit by use of CK subunits (molecular weight, 56 kd and 64 kd) isolated from the stratum corneum of human epidermis.

I would like to rebut the comments from Dr Ophir. First, he said that CK immunoreactivity is found throughout the thickness of the olfactory epithelium. Our unpublished data have shown that only in occasional cases, all cell layers of the epithelium appeared to react to the anti-CK antiserum. In these specimens, however, only the intercellular spaces (not the intracellular) of the epithelium were immunolabeled. The same immunoreactivity was seen in control specimens. Such immunoreactivity was suspected to be a nonspecific reaction.

Second, electron microscopic observations demonstrated that tonofilaments composed of CK are rich in the cytoplasm of basal cells,[1] but not present in that of olfactory receptor cells and supporting cells. Do cells that are lacking in tonofilaments have immunoreactivity for CK?

Third, when the olfactory epithelium was replaced by keratinized squamous epithelium in a case of olfactory disturbance, all cells in the epithelium reacted to the same anti-CK antiserum used in the present study.[2] It is obvious that the antiserum we used can stain all cells in the olfactory epithelium if the cells have sufficient tonofilaments in their cell bodies.

In conclusion, I believe that CK is restricted to basal cells in the olfactory epithelium.

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ANNALS

OF OTOLOGY, RHINOLOGY & LARYNGOLOGY

ANNALS OF HEAD & NECK MEDICINE & SURGERY

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POSTERIOR SEMICIRCULAR CANAL OCCLUSION FOR INTRACTABLE BENIGN PAROXYSMAL POSITIONAL VERTIGO

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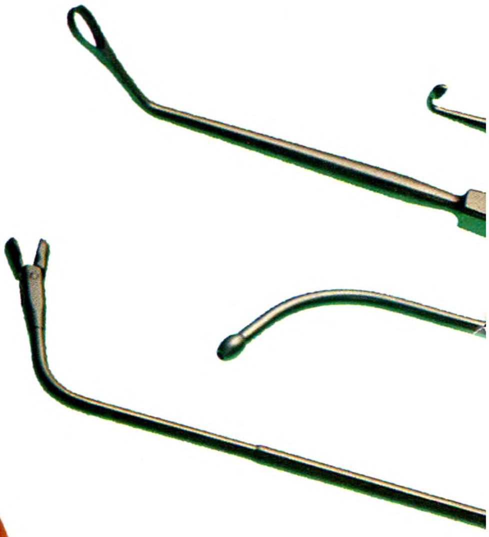

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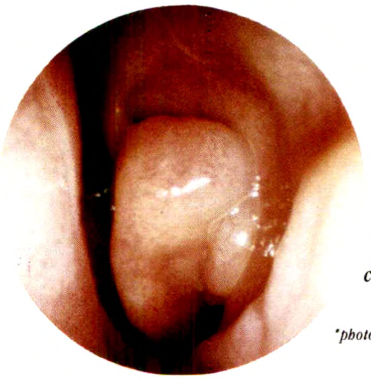
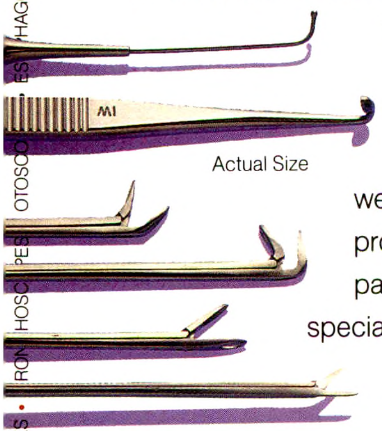


*Concha bullosa on left side bulging into lateral nasal wall. Entrance to middle meatus blocked and a polyp is arising from the contact area.**

**photo by Professor H. Stammberger*



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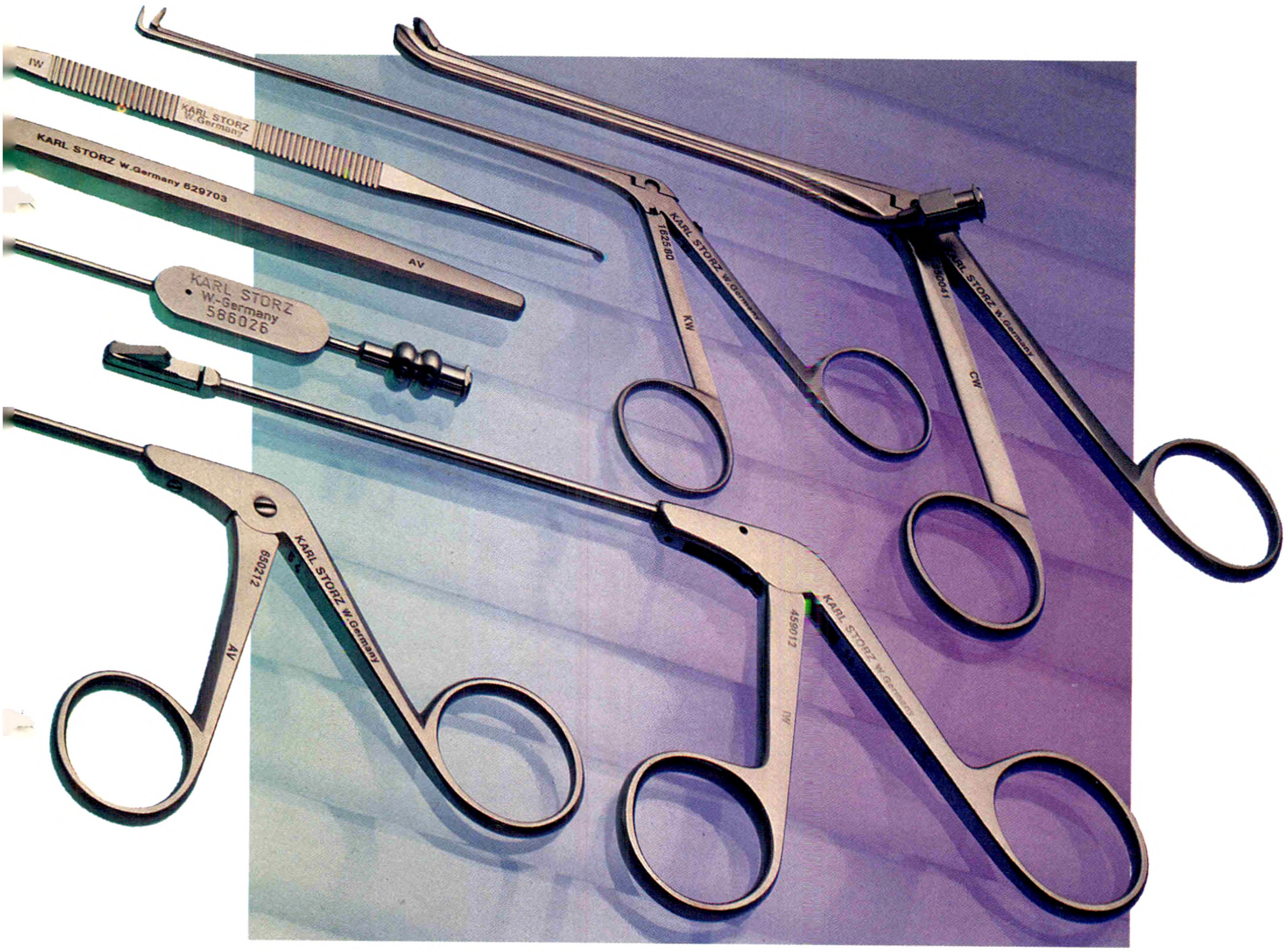
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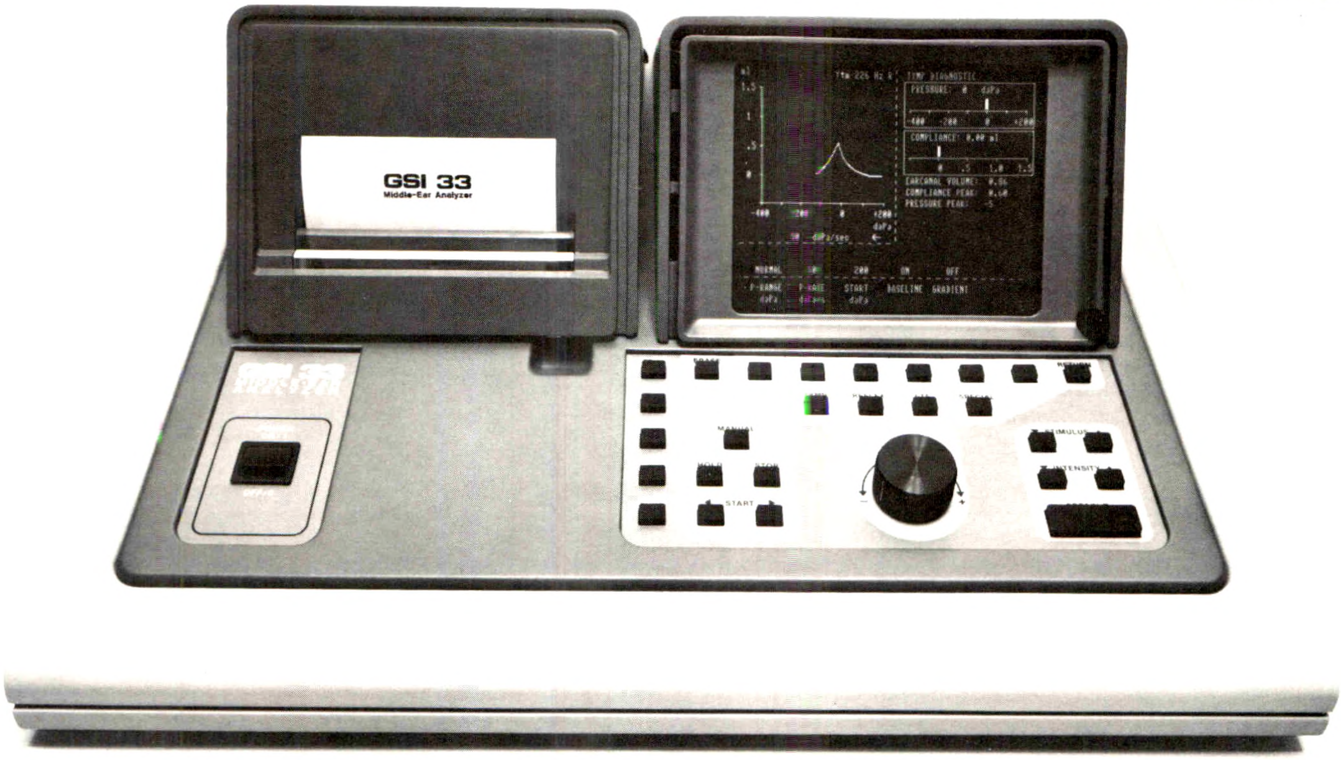

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January 1990

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PATHOLOGIC FINDINGS IN THE LABYRINTHINE SEGMENT OF THE FACIAL NERVE IN A CASE OF FACIAL PARALYSIS

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The histopathologic findings for a patient with acute facial paralysis caused by herpes zoster oticus who obtained no return of active facial function after 1 year are presented. All imaging studies were nondiagnostic. Biopsy of the labyrinthine segment was performed. Histopathologic analysis showed a sharp line of demarcation between sclerotic nerve proximal to and necrotic nerve distal to the meatal foramen area of the fallopian canal. This finding is consistent with observations that the lesion producing Bell's palsy and herpes zoster oticus usually is situated at the meatal foramen.

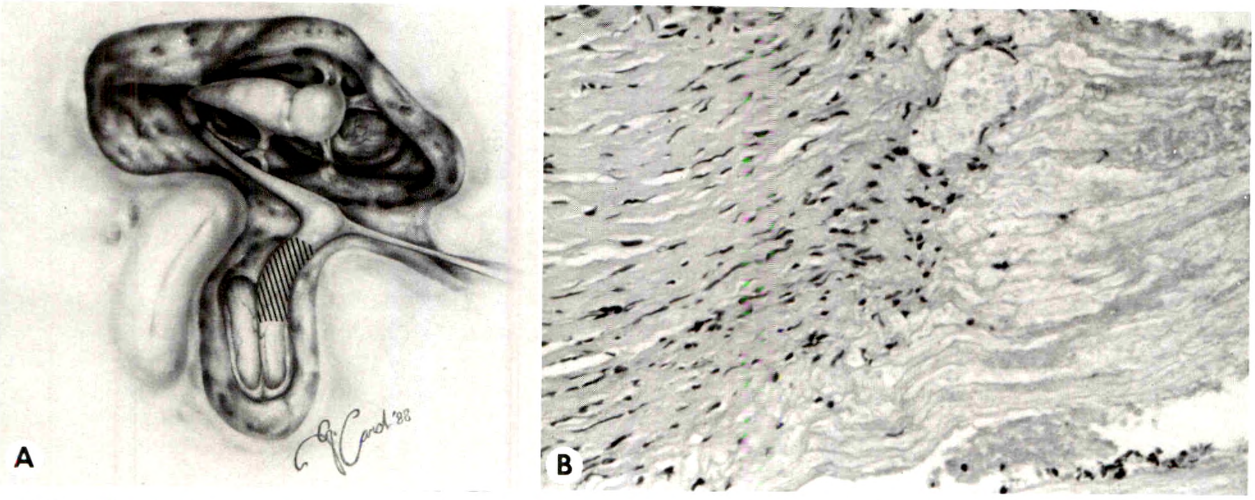
KEY WORDS — facial paralysis, herpes zoster oticus.

INTRODUCTION

The major controversy today in the management of the patient with idiopathic acute peripheral facial palsy is whether patients with poor prognostic tests should undergo surgical decompression of the facial nerve. Since 85% of patients with Bell's palsy will experience a satisfactory return of facial function with no treatment,[1] electrodiagnostic tests are used to identify those patients with extensive degeneration and a high probability for poor functional return. Fisch[2] has recommended decompression when degeneration reaches 90% to 94% by electroneurography within 3 weeks of onset of paralysis. Intraoperative evoked electromyography (EMG) has shown that the lesion producing Bell's palsy is located at the meatal foramen of the fallopian canal in 94% of patients.[3] Therefore, decompression is initiated at or confined to the labyrinthine segment by use of a middle fossa approach.

The location of the lesion in Bell's palsy at the meatal foramen (the entrance of the fallopian canal at the fundus of the internal auditory canal) is consistent with the known anatomy of this region. The loosely arranged intrameatal fibers of the facial nerve are constricted in the meatal foramen to form a fibrous ligament.[2] The meatal foramen is approximately 0.61 mm in diameter[4] and is the narrowest portion of the fallopian canal. Fisch[2] has referred to this area as a "physiologic bottleneck," in which the facial nerve fibers are literally strangulated in the presence of inflammatory edema.

The facial paralysis associated with herpes zoster oticus has, in general, a worse prognosis than that



Labyrinthine section of facial nerve. A) Schematic of middle fossa exposure. Shaded area — biopsied segment of facial nerve. B) Facial nerve at point of constriction in meatal foramen of fallopian canal (H & E, original x400). Left side of photograph shows essentially normal nerve, with sharp demarcation from necrotic, fibrotic anuclear nerve fragment on right.

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caused by Bell's palsy.[5] Although the cause of the edema is different in these two conditions, the location of the nerve conductivity block, as measured by intraoperative evoked EMG, is the same, ie, the meatal foramen.[4] This localization has been explained by both anatomic and electrophysiologic studies, but there has been no histopathologic confirmation. A case of a patient with herpes zoster oticus that resulted in a poor return of function is presented. Biopsy of the labyrinthine segment of the facial nerve demonstrated a sharp demarcation between sclerotic and necrotic nerve at the meatal foramen.

CASE REPORT

The patient is a 33-year-old woman who developed an acute, complete left facial palsy accompanied by ear pain, aural vesicles, and dizziness. She had no hearing loss. Her facial paralysis persisted without improvement for 6 months, when facial nerve stimulation testing elicited no response on the left at 6.5 mA. The nerve appeared normal on transmastoid facial nerve decompression, but no return of function was observed after 6 months.

She was referred to The Otology Group, PC, where 1 year after the onset of paralysis she exhibited a complete left facial paralysis. There was no response on the left to maximal stimulation electrical testing. Electromyography indicated total denervation of facial musculature with no signs of regeneration. Results of audiometry and auditory brain stem response testing were normal. High-resolution computed tomograms of the temporal bone and magnetic resonance images of the posterior fossa and intratemporal facial nerve were normal except for changes from the transmastoid decompression.

The lack of facial nerve function after 1 year demanded exploration of the facial nerve despite nondiagnostic imaging studies. When the labyrinthine and internal auditory canal segments of the facial nerve were explored through a middle fossa approach, the intratympanic and internal auditory canal segments of the nerve appeared normal. However, the labyrinthine segment had the appearance of devitalized nerve. A biopsy sample of the labyrinthine segment was taken (see Figure, A), and there was no evidence of tumor on frozen section. A hypoglossal-facial nerve anastomosis then was performed.

HISTOPATHOLOGY

The permanent hematoxylin and eosin–stained histologic sections from the facial nerve biopsy sample (labyrinthine section at the meatal foramen of the fallopian canal) showed a sharp demarcation of the proximal portion of the nerve, in which there was essentially normal histology except for a slight sclerotic appearance. Schwann cells and perineural connective tissue were prominent in the normal nerve section and were differentiated from the distal nerve portion, in which there was a mixed fibrotic and necrotic anuclear micromorphology. There were scattered collections of small, round inflammatory cells within the distal necrotic nerve segment (see Figure, B).

DISCUSSION

Most of the histopathologic findings reported with Bell's palsy and herpes zoster oticus are the result of postmortem studies. May et al[1] note that degeneration, hemorrhage, and inflammatory infiltrates are present in the facial nerves of patients who had idiopathic palsy and herpes zoster oticus. Fowler[6] described the findings for the facial nerve of a patient 14 days after onset of paralysis who had chronaxie studies indicating complete degeneration of all muscles supplied by the paralyzed facial nerve. There were fresh hemorrhages in the internal auditory canal between the region of Scarpa's ganglion and the narrow bony channel of the porus acousticus. Also noted in this region were neural sheaths that looked swollen and empty.

It is difficult to interpret the significance of these researchers' findings, since there is great variability in the duration between onset of facial paralysis and death and in the severity of paralysis. There are very few reports in which degree of palsy and results of prognostic tests are available.[1] We are unaware of any reports of the histopathologic findings of the labyrinthine segment of the facial nerve in a patient with test results indicating a poor prognosis (ie, with greater than 90% degeneration by evoked EMG or complete lack of stimulation by maximal stimulation testing).

The histopathologic analysis of the facial nerve in our patient is limited to the labyrinthine segment. Since there was complete degeneration of the facial nerve at the time of exploration, we could not confirm the area at the meatal foramen as the location of the block by intraoperative evoked EMG. The presence of a sharply demarcated junction between identifiable nerve fibers and necrotic nerve at the meatal foramen of the fallopian canal is highly suggestive that this is the location of the nerve conductivity block. These findings are consistent with Fisch's designation of this area as a physiologic "bottleneck" and would support the logic of performing surgical decompression specifically directed at the labyrinthine segment via the middle fossa approach. Efficacy is yet to be established, but preliminary data are encouraging.[7]

SUMMARY

The identification of a sharply defined demarcation between identifiable nerve fibers and necrotic nerve at the meatal foramen of the fallopian canal in a patient with herpes zoster oticus is histopathologic confirmation of the concept of strangulation of the nerve fibers at this narrow junction in the presence of edema. The rationale for a surgical decompression directed to the labyrinthine segment is supported.

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EDITOR'S COMMENTS

This is a landmark paper and will be widely cited in the future. For the first time, pathologic evidence is established that the precise point of the lesion in a case of facial paralysis in a disease producing edema of the nerve is in the narrowest part of its bony tube, the meatal segment (as Fisch postulated). The great importance of this discovery is that it puts nearly the last brick into place in the long construction of the surgical decision as to where decompression should be carried out: not in the vertical course of the nerve, but in the meatal segment.

Otology is enriched by this paper.

Brian F. McCabe, MD
Editor

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XX INTERNATIONAL CONGRESS OF AUDIOLOGY

The XX International Congress of Audiology will be held October 14-18, 1990, in Tenerife, Canary Islands, Spain. For further information, contact Dr Jose Barajas, Presidente, C/Perez de Rozas, 8, 38004 Santa Cruz de Tenerife, Canary Islands, Spain; telephone 22 27 54 88; telex 91106.

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POSTERIOR SEMICIRCULAR CANAL OCCLUSION FOR INTRACTABLE BENIGN PAROXYSMAL POSITIONAL VERTIGO

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Benign paroxysmal positional vertigo (BPPV) is most often a self-limited disorder arising from the posterior semicircular canal of the undermost ear in the Hallpike position. Some individuals with this disorder have severe and protracted symptoms requiring more than expectant therapy. We describe two patients with intractable BPPV and profound sensorineural hearing loss in the affected ear treated by transmastoid posterior semicircular canal occlusion. Postoperatively, both were relieved of their BPPV and demonstrated preserved lateral semicircular canal function as measured by electronystagmography. We feel this new procedure provides a simpler and possibly safer alternative to singular neurectomy and should be given future consideration in the treatment of intractable BPPV in a normal-hearing ear.

KEY WORDS — benign paroxysmal positional vertigo, cupulolithiasis, posterior semicircular canal occlusion.

INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is a common vestibular end organ disorder. In one busy vestibular clinic it was diagnosed in 17% of patients.[1] It is most often an idiopathic or degenerative disorder, occurring frequently in the middle to late decades.[2] Head trauma, the second most common cause, underlies most cases of bilateral BPPV.[3] Other, less frequent causes include viral labyrinthitis, vestibular neuronitis, stapedectomy, perilymph fistula, and Meniere's disease.[4]

The pathologic site of BPPV has been localized to the posterior semicircular canal.[5] Schuknecht and Ruby[6] found large basophilic deposits (presumably displaced otoconia) attached to the posterior semicircular canal cupula on examination of postmortem temporal bones from patients with clinical BPPV. They coined the term cupulolithiasis to describe this finding. The Hallpike maneuver rotates the posterior semicircular canal of the undermost ear in the earth vertical plane. The classic findings with left-sided involvement are a clockwise rotatory nystagmus in the left head-hanging position, and with right-sided involvement, a counterclockwise rotatory nystagmus in the right head-hanging position. Although various combinations of rotatory, vertical, and oblique eye movements have been described depending upon the position of the globe within the orbit, the nystagmus profile correlates with the known neuromuscular pathways arising from the posterior canal of the undermost ear.[5,7-9]

Most cases of BPPV, particularly the posttraumatic variety, are self-limited. However, the course often can be protracted, with up to one third of patients in a large series reporting symptoms dating back for more than 1 year.[4] Not uncommonly, the chronic cases may demonstrate periods of exacerbation and remission. When the disease is very active, in addition to the brief episodes of vertigo associated with position change, patients may complain of protracted nonspecific imbalance and dizziness accompanied by mild lassitude.

As most cases of BPPV are self-limited, we treat our patients expectantly. If severe symptoms persist unchanged for greater than 1 year, then it is probable that the BPPV is permanent, and a diagnosis of cupulolithiasis is made. If the symptoms have a significant effect upon the patient's life-style or occupation, we feel that operative intervention is indicated. The mainstay of operative treatment has been the singular nerve section described initially by Gacek.[10] Singular neurectomy selectively eliminates posterior semicircular canal function. However, as Silverstein[11] pointed out, singular neurectomy is a very difficult operation to learn and has a significant risk of failure and sensorineural hearing loss in inexperienced hands. In a recent human temporal bone study, Ohmichi et al[12] demonstrated that the singular nerve was inaccessible through a tympanotomy approach in 14% of the bones examined. These nerves were shielded by the labyrinth, and successful singular nerve section in such cases likely would ravage the inner ear.

Money and Scott[13] developed a technique in cats that involved plugging individual semicircular canals. They established that plugging a semicircular canal completely blocked its receptivity without influencing the functions of the other vestibular receptors. On the basis of the findings of Money and Scott, we postulated that the symptoms associated with cupulolithiasis could be relieved by posterior semicircular canal occlusion on the affected side. Posterior semicircular canal occlusion through a transmastoid approach would be a simpler and possibly safer alternative to a singular neurectomy. Of concern was the possibility of cochlear damage with this procedure, and Money and Scott had not addressed this possibility in their study. To examine

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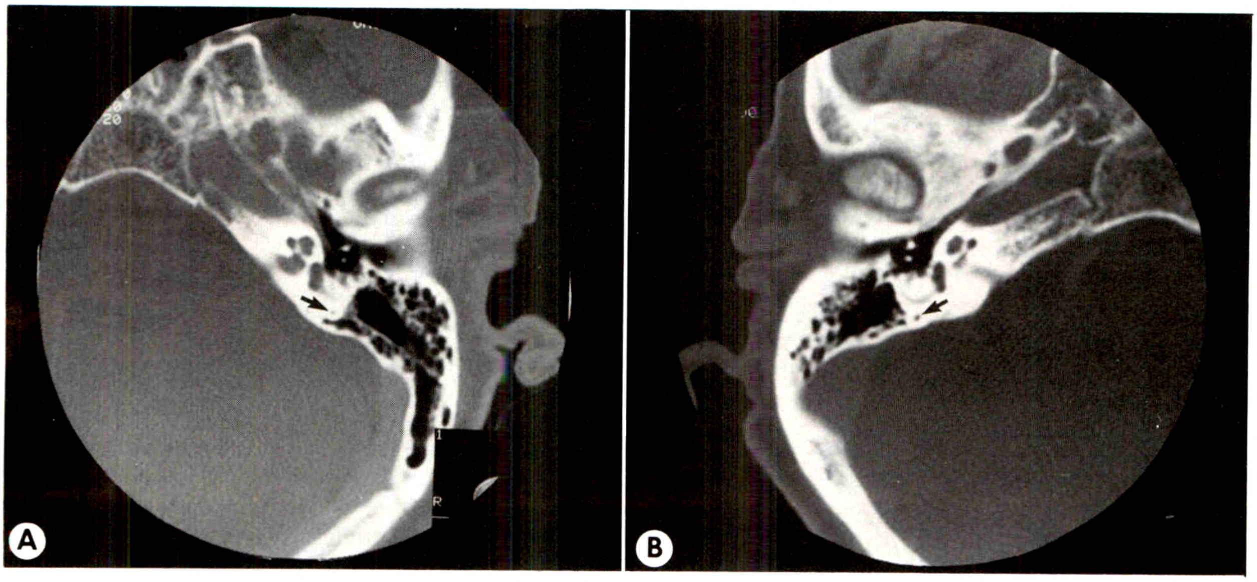

Fig 1. Preoperative computed tomograms of temporal bones, showing areas of posterior semicircular canal to be occluded (arrows). A) (Case 1) Left temporal bone. B) (Case 2) Right temporal bone.

these effects, a study was carried out on guinea pigs in which brain stem auditory evoked responses were measured before and after posterior canal occlusion.[14] The canal occlusion was obtained by making a small "puncture" through the posterior semicircular canal with a diamond bur. This action resulted in simultaneous plugging of the adjacent canal ends with impacted bone chips. With this procedure, there was minimal effect on the brain stem evoked auditory responses, suggesting no cochlear damage. With this background, the transmastoid posterior canal occlusion technique was carried out on two patients with intractable BPPV.

CASE REPORTS

Case 1. This 70-year-old woman presented with a 2-year history of positional vertigo. At the age of 68, she suddenly lost hearing in the left ear. The following day she experienced sudden onset of vertigo, along with nausea and vomiting. The intense vertigo persisted for the next 3 days and was made worse by any head movement. Following resolution of the intense steady vertigo, she continued to experience short-lived (30 seconds) episodes of vertigo associated with changes in head position such as getting out of bed, lying on her left side, or rolling over in bed. She found it difficult to perform normal household duties because of the exquisite sensitivity of the disorder, which often was triggered by the slightest head movement either up or down and to the left. She had a persistent nonpulsatile roaring tinnitus in her left ear and no recovery of hearing.

Physical examination revealed a severe sensorineural hearing loss in the left ear. On the Hallpike test in the left head-hanging position after a 3-second latency she developed a violent clockwise rotatory nystagmus lasting 20 to 30 seconds. On her returning to the sitting position, a milder counterclockwise nystagmus with latency was seen. Her symptoms of vertigo and nausea were replicated perfectly with this maneuver. The vertigo and nystagmus were absent with a second Hallpike maneuver during individual examinations, but were reproduced easily during four different visits.

Her audiogram revealed a profound left-sided sensorineural hearing loss and normal hearing on the right. On electronystagmography (ENG) with horizontal leads, there was no spontaneous or positional nystagmus. Hot (44°C) and cold (30°C) caloric stimulation produced peak slow phase velocities of 53°/s and 27°/s, respectively, in the right ear, and 68°/s and 31°/s, respectively, in the left ear. Axial computed tomograms of the left temporal bone were normal and demonstrated a well-pneumatized mastoid (Fig 1A). A diagnosis of cupulolithiasis was made. Various treatment options were discussed with the patient, and she wished to pursue operative intervention. With a complete hearing loss in the affected ear, she was an ideal first candidate for posterior semicircular canal occlusion.

We used the original canal "puncture" technique as outlined in our guinea pig study.[14] Following the "puncture," perilymph continued to ooze through the impacted bone chips. This did not occur in the guinea pig model, probably because of the smaller size of the canal. The puncture was sealed with human fibrinogin glue (Tisseel; Immuno AG, Vienna) and a layer of fascia, which checked the perilymph leak. Postoperatively, the patient experienced severe vertigo for 1 week, which was aggravated by all head movements. There was a slight pendular type horizontal/rotatory nystagmus that resolved over 1 week.

Four days postoperatively, the ENG showed moderate impairment of both saccadic and smooth pursuit movements but no spontaneous nystagmus with eyes closed. Surprisingly, there was no response to cold caloric stimulation on either side. The ENG at 7 days again showed absence of spontaneous nystagmus with eyes closed, and no positional nystagmus. Cold caloric stimulation showed improved responses of 20°/s on the left and 23°/s on the right.

The patient was discharged on the 11th postoperative day, and by day 17 she was starting to return to her normal daily activities. At this time the results of her first postoperative Hallpike test proved to be completely negative for nystagmus and vertigo. An ENG showed normal saccadic and smooth pursuit movements with absence of gaze nystagmus. Cold calorics had improved to 26°/s on the left and 35°/s on the right. After 1 year she continues to be symptom-free and describes an overall improvement in well-being compared to her preoperative state. She describes an increased energy level with freedom from the chronic vague imbalance sensation she had experienced preoperatively between her major vertigo spells.

Case 2. This 57-year-old woman presented with a 2½-year history of positional vertigo. At the age of 54 she presented to another otolaryngologist with a gradual progressive right-sided hearing loss. A presumptive diagnosis of otosclerosis was made, and she underwent a stapedectomy with prosthesis. Postoperatively her hearing was much worse, and 6 months later a revision was attempted. Immediately following this revision, she experienced her first spell of positional vertigo that persisted despite a second attempted revision 6 months later. As well, she noted a complete loss of hearing in the operative ear after the first revision, with no improvement following the second revision.

Her attacks of vertigo occurred daily. They were provoked by certain head movements and lasted a maximum of 20 seconds. The vertigo was most distressing at her workplace, a canning factory in which she was a supervisor. Her work entailed frequent bending and lifting that often triggered the vertigo. With time she found the constant attention required to avoid these spells was significantly restricting her job performance, and she was therefore referred to our institution for operative intervention.

Physical examination demonstrated a severe right-sided sensorineural hearing loss. On the Hallpike test in the right head-hanging position, following a latency period of 3 seconds, she developed a violent counterclockwise rotatory nystagmus lasting approximately 20 seconds. There was a reversal of the nystagmus, but of less intensity, with an initial latency period of 2 to 3 seconds upon her returning to the sitting position. The response, which fatigued on repeat testing, also was demonstrated on two other clinic visits.

An audiogram showed a profound sensorineural hearing loss in the right ear and normal hearing in the left. The ENG with horizontal leads showed an absence of spontaneous or positional nystagmus. Caloric responses on the left were 74°/s and 56°/s following hot and cold stimulation. Right-sided calorics were 41°/s after both hot and cold stimulation. The CT showed normal findings, including a moderately well-pneumatized mastoid (Fig 1B).

A diagnosis of cupulolithiasis was made, and after a long, careful discussion about various treatment options, the patient wished to pursue transmastoid posterior semicircular canal occlusion. The occlusion technique was modified from the original "puncture." A 2- to 3-mm posterior canal segment was blue-lined through 180° around the outer turn. The endosteum was opened with a small 90° hook, with care taken not to aspirate the inner ear fluids. Bone paste from the mastoidectomy was delivered into the opening in a gentle but firm fashion with the intention of compressing the membranous labyrinth while maintaining its integrity. A layer of bone wax plus a second layer of fascia stopped the perilymph leak.

This patient's postoperative course was considerably more tolerable. There was no spontaneous vertigo or nystagmus throughout the postoperative period. Certain head movements such as sitting up or lying down continued to make her vertiginous for the first 5 or 6 days. A Hallpike test on the third postoperative day showed the same preoperative nystagmus but with much less intensity. She was now ambulating and was discharged on her fifth postoperative day. She continued to improve symptomatically, and by day 8 the Hallpike test showed a further reduction of the induced nystagmus intensity. The ENG showed absence of a spontaneous or gaze nystagmus. Caloric responses to hot and cold stimuli were now 98°/s and 48°/s on the left and 21°/s and 26°/s on the right.

On follow-up 2 weeks later, she reported complete absence of vertigo despite provocative efforts. Her mild imbalance continued to improve on a daily basis. The results of the Hallpike maneuver were now completely negative, and the results on ENG were essentially unchanged from those of the previous study. She remains symptom-free after 9 months of follow-up.

DISCUSSION

The preliminary results from these two patients suggest that posterior semicircular canal occlusion can relieve the symptoms associated with intractable BPPV, or what many refer to as cupulolithiasis. Hall et al[15] divided BPPV into fatigable and nonfatigable types and suggested that free-floating particles caused the former and that particles fixed

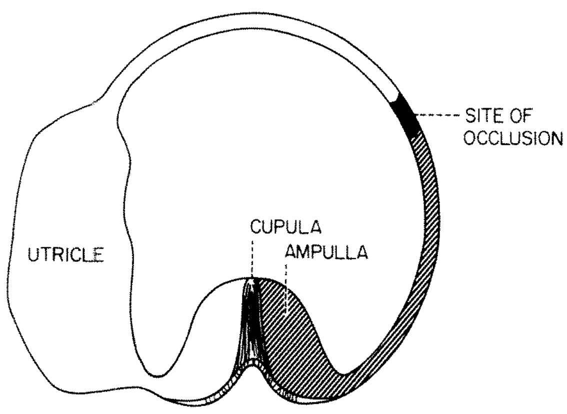

Fig 2. Schematic representation of occluded posterior semicircular canal. Shaded area — closed fluid (endolymph)- filled space between impermeable cupula and site of occlusion.

to the cupula caused the latter. It was suggested that a fatigable and nonfatigable classification could provide the diagnostic criteria separating BPPV that subsides spontaneously from cupulolithiasis. As both patients in this study had fatigable BPPV, one for 2 years and the other for 2½ years, it seems more appropriate to classify BPPV on the basis of duration of symptoms. If symptoms persist unchanged for greater than 1 year, the BPPV is unlikely to resolve, and the diagnosis of cupulolithiasis is made. The patient becomes a potential candidate for posterior semicircular canal occlusion.

Conventional theory explains the signs and symptoms of BPPV on the basis of endolymph flow, and in turn cupular deflection, when loose particles in the endolymph of the posterior semicircular canal move under the influence of gravity. Similarly with cupulolithiasis, a mass on the cupula can move under the influence of gravity and induce cupular deflection. In either case, cupular deflection implies endolymph displacement. However, with the semicircular canal occluded, a closed fluid-filled space is created between the site of occlusion and the cupula, as illustrated in Fig 2. Since fluid cannot be compressed or expanded, the closed fluid-filled space acts as a solid member, and the cupula becomes fixed.

Singular neurectomy eliminates the resting discharge from the posterior canal, creating a static asymmetry[16] between the two posterior canals. In this situation, one would anticipate persistent vertigo along with rotatory/vertical spontaneous nystagmus with the patient at rest. Posterior canal occlusion does not disturb the resting discharge from the occluded canal, so one would not expect symptoms with the patient at rest, as demonstrated in the second patient. However, the first patient did develop a spontaneous nystagmus. We suspect that trauma from the canal "puncture" caused a labyrinthitis resulting in temporary canal paresis, and this would be supported by the reduced caloric response. The simultaneous reduction in caloric response on the opposite side is difficult to explain, but may represent some form of cerebellar clamp.[17]

With both singular neurectomy and posterior canal occlusion, head movement produces a dynamic asymmetry.[16] One would expect symptoms from posterior canal stimulation, and this proved to be the case with both patients. The dynamic asymmetry appeared to adapt completely within a few weeks.

We opted to change the occlusion technique in the second patient for three reasons. The first was to minimize the amount of canal trauma and reduce the degree of labyrinthitis. The second reason related to the anatomy of the mastoid. The mastoid in the second case was less pneumatized than in the first (Fig 1), and the posterior semicircular canal was sitting flush against the cerebellar plate. A technique was required that would avoid inadvertent breach of the posterior fossa dura during the canal puncture. The third reason was more theoretic, and related to future canal occlusions in normal-hearing patients. We felt that drilling through endolymph and perilymph was likely to be more traumatic to the organ of Corti than drilling on otic capsule bone alone. The "compression" technique used for the second case proved to be just as effective as the original "puncture."

The transmastoid approach provides easy access to the posterior semicircular canal for occlusion. In creating the occlusion, we stress the importance of using bone chips to promote new bone formation[18] leading to complete permanent occlusion of the canal. We have shown in two patients that posterior semicircular canal occlusion can relieve intractable BPPV (cupulolithiasis) and at the same time preserve lateral semicircular canal function. The effect of canal occlusion on hearing in the otherwise normal human ear is unknown. However, since animal studies[illegible] indicate no deleterious effect on hearing, we feel that this procedure now should be given consideration in the treatment of the normal-hearing ear with BPPV.

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MIDDLE EAR GAS GENERATION IN MYRINGOPLASTIES

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No Gelfoam was used to support the vein in 10 simple underlay vein graft myringoplasties. Computed tomographic studies 24 hours postoperatively showed gas filling 75% to 100% of the middle ears in three ears. The epitympanum and mastoid were also evaluated. Apparently, in some ears the middle ear generates gas in the immediate postoperative period to support fresh vein grafts.

KEY WORDS — gas generation, middle ear, myringoplasty.

For 25 years the author has performed simple vein graft myringoplasties by the underlay technique without using Gelfoam in the middle ear to support the graft, but relying on middle ear–generated gas, blood, and serum to hold the grafts in place. Gelfoam is placed in the external canal to prevent any external herniation of the freshly placed grafts. The postoperative results have been satisfactory, with 90% to 95% graft takes.

To determine if gas or blood clot filled the middle ear with use of this technique, 10 consecutive myringoplasties were studied by computed tomography (CT) 24 hours postoperatively. The ears were scanned axially through the bone window, and the relative amounts of gas, blood, and serum were estimated visually in three areas: the middle ear, the epitympanum, and the mastoid.

Seven ears were scanned preoperatively. Otoscopically, all 10 ears were dry and free of discharge. All 7 ears scanned by CT were free of fluid and air-filled. In 3 cases the mastoid was small and sclerotic.

RESULTS

The results are shown in Fig 1 as percentages of the respective segments of the temporal bone that were filled with air. Two middle ears were completely air-filled. In one ear the vein graft appeared to be ballooned externally (Fig 2). In one ear the middle ear was 75% air-filled. One ear was 40% air-filled, and one, 30%. Five middle ears were partially or completely fluid-filled: two were 20% air-filled; one, 10%; and two had no air whatsoever.

The mastoid air cells were normally developed and aerated in seven ears. In the three small sclerotic mastoids the postoperative middle ear aeration was 30%, 20%, and 0% (cases 5, 6, and 9).

The epitympanums of seven ears were 100% air-filled; of one ear, was 50% aerated; and of two ears, were fluid-filled. Five mastoids were aerated 100%; two, 80%; and one, 30%; while two were completely cloudy. One of the completely cloudy mastoids without evidence of any air had a 75%-aerated middle ear. This ear was not scanned preoperatively.

Nine of the grafts healed without perforations, although after 2 years three grafts were not yet covered with cornified epithelium. The failure occurred in an ear previously operated on that had suffered a hot-weld spark slough of the tympanic membrane. The postoperative CT scan in this ear

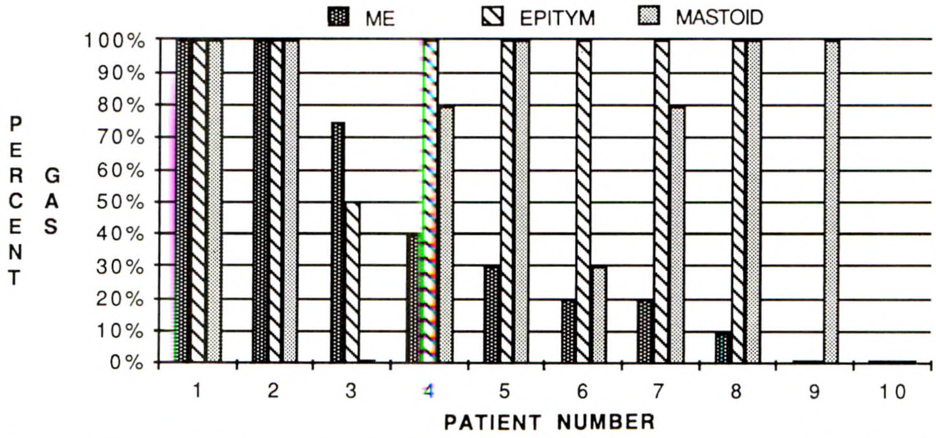

Fig 1. Graph showing relative amounts of gas versus fluid in middle ear (ME), epitympanum (EPITYM), and mastoid segments of ear.

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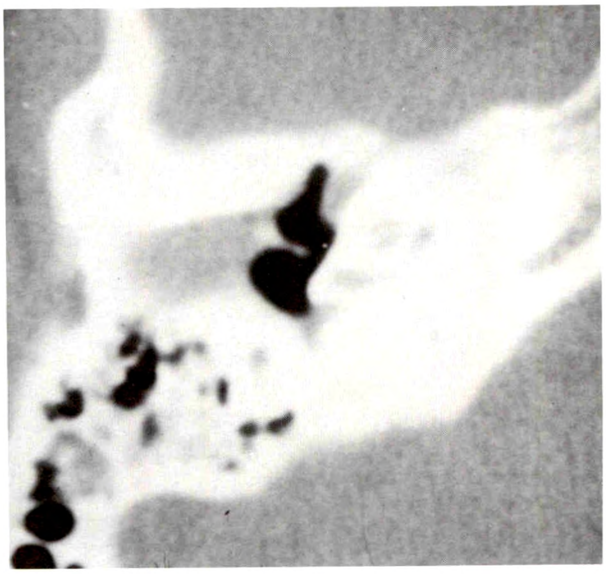

Fig 2. (Case 2) Axial computed tomographic scan performed 24 hours after vein graft myringoplasty. Middle ear is completely filled with air. Medial surface of graft appears to be herniated laterally. Mastoid air cells are air-filled.

showed complete cloudiness of the middle ear, epitympanum, and mastoid process (patient 10).

DISCUSSION

The results of this study indicate that not all myringoplasties without Gelfoam graft support fill with blood and serum, but instead, some remain gas-filled for at least 24 hours after operation.

Further, it appears that in at least three ears, two with 100% and one with 75% aeration, another mechanism of middle ear ventilation exists that is not consistent with the current theory of eustachian tube function. Current theory assumes that gas is absorbed in the middle ear, forcing the tympanic membrane medialward and developing a pressure gradient from nasopharynx to middle ear.[1] With swallowing, the eustachian tube opens, permitting the elasticity of the retracted tympanic membrane to draw air into the middle ear to equalize the pressure differential produced by the gas absorption. In the present series the fresh vein grafts were apposed, unsupported by Gelfoam, to the medial surface of the tympanic membrane remnant. If gas had been absorbed and a pressure differential generated, the grafts should have pulled away from the graft bed and necrosed.

Parenthetically it should be noted that Gelfoam is not used to support the endomeatal flap following stapedectomies. A negative pressure gradient caused by oxygen absorption should displace the freshly replaced tympanic membrane and flap medially, at least during the early postoperative period, as inward pull is exerted on the membrane.

While performing tympanoplasties without Gelfoam to support vein and connective tissue grafts, the author has noted that under local anesthesia the fresh grafts tend to balloon externally when the endomeatal flap is repositioned and the middle ear is sealed from the atmosphere. It is well known that nitrous oxide diffuses into the middle ear during general anesthesia, and many surgeons order nitrous oxide administration stopped before they begin to position grafts in the ear.[2,3]

In the three middle ears in this series 100% and 75% filled with gas, pressure generated in the middle ear was sufficient to hold the grafts in place until they healed.

The author and his associates have demonstrated the presence of positive pressure in noninflamed perforated tympanic membranes by sealing the perforation with a film of sterile oil-based medication.[4] Using the tympanometer, Hergils and Magnuson,[5,6] Shinkawa et al,[7] and Sadé and Luntz[8] have shown that the normal middle ear generates a slight positive pressure following sleep. A recent study by Takahashi et al,[9] using a pressure transducer passed into the middle ear via the eustachian tube, confirmed the slight increases in middle ear pressure over atmospheric pressure in the normal ear.

The results of this study indicate that gas slightly above atmospheric pressure in an amount sufficient to maintain a fresh graft in contact with the graft bed is generated in some ears following simple myringoplasty.

ACKNOWLEDGMENT — The author thanks Stasia J. Frank, MD, Head of Special Imaging Services, Resurrection Hospital, Chicago, Illinois, for her assistance in this study.

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MINICRICOTHYROTOMY FOR TRACHEOBRONCHIAL TOILET

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Thirty-six patients underwent percutaneous cannulation of the cricothyroid membrane, using a small endotracheal tube, for the purpose of repeated suction of secretions from the tracheobronchial tree. The duration of cannulation ranged from 4 to 62 days (average, 12 days). Twenty-eight patients were followed up for a maximum of 3.5 years (mean, 20 months). There were no immediate or delayed postoperative complications. Subglottic stenosis did not occur in any of the patients. Minicricothyrotomy is a relatively safe and simple and efficient technique for tracheobronchial toilet in patients with chronic lung disease and in the postoperative period.

KEY WORDS — cricothyrotomy, sputum retention, tracheobronchial toilet.

Retention of tracheobronchial secretions is an important cause of morbidity and mortality during the postoperative period and in patients with chronic lung disease. At especially high risk are those patients who are incapable of adequately clearing their secretions following thoracic surgery and neurosurgery. Existing methods of management of sputum retention, although applicable in some cases, have certain disadvantages: they may be only partially effective (nasotracheal "deep" suction, physiotherapy), unsuited for repeated use at short intervals (bronchoscopy), or accompanied by significant morbidity (nasotracheal intubation, tracheotomy). The lack of convenient and ready access to the trachea for suction may result in delayed treatment, thus leading in turn to bronchopneumonia, respiratory failure, and death.

We present a relatively simple method of percutaneous cannulation of the cricothyroid membrane by use of a small Portex endotracheal tube that enables repeated and efficient suction of secretions from the tracheobronchial tree with minimal morbidity.

TECHNIQUE

We customize a cricothyroid cannula from a soft, uncuffed, Portex pediatric endotracheal tube of 4 or 4.5 mm diameter. The optimal tube length for a normal adult was found to be 12 cm, of which 8 cm is inserted percutaneously into the trachea. The 4-cm-long external portion of the tube is split down the middle, and the wings thus formed are opened out in opposite directions over the anterior surface of the neck. A wire guide inserted through the tube serves as an internal splint, preventing the tube from impinging upon the posterior tracheal wall or bending as it is moved into position (Fig 1).

The patient is positioned supine with the neck extended. After the skin is cleansed, the position of the cricothyroid membrane is located by palpating the prominent arch of the cricoid cartilage. In the average adult this is 2 to 3 cm below the notch of the thyroid cartilage. Lidocaine hydrochloride 1% is infiltrated under the skin, and a horizontal 1-cm skin incision is made just above the upper border of the cricoid cartilage. By placement of the incision close to the cricoid cartilage, hemorrhage from the cricothyroid arteries can be avoided. Care should be taken not to cut through the anterior jugular veins, which sometimes run close to the midline and tend to be congested in patients with congestive heart failure. After the muscle fibers are separated with a hemostat, the cricothyroid membrane is punctured with an 18-gauge needle attached to a 10-mL plastic syringe containing 2 mL saline, with negative pressure exerted via the plunger. The passage of air bubbles from the tracheal lumen into the syringe indicates that the direction is correct. This is important, because the cricothyroid membrane is triangular in shape, and one therefore must make sure that the needle is directed through the membrane and into the airway, rather than tangentially to it. A small incision is made in the cricothyroid membrane by use of the needle as a

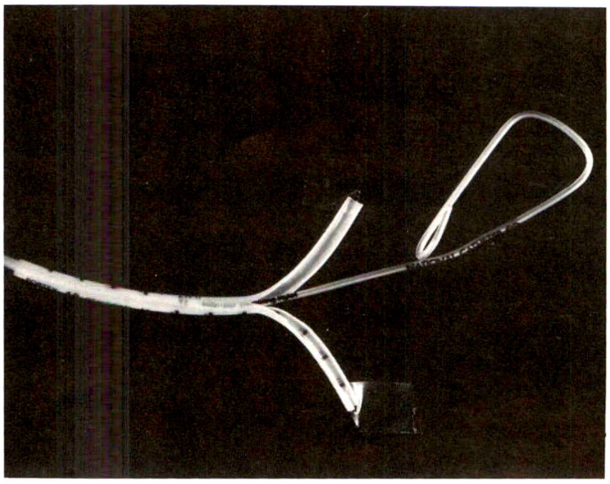

Fig 1. Four-millimeter endotracheal tube adapted for minicricothyrotomy with wire guide inserted.

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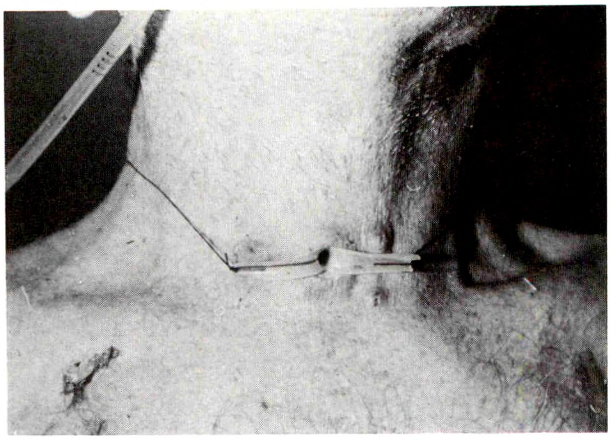

Fig 2. Minicricothyrotomy cannula in place.

guide, and then the wound is enlarged laterally by insertion of a thin hemostat. Once a hole is made in the cricothyroid membrane, the custom-fitted tube with its wire guide is advanced into the trachea; when correctly placed it encounters no resistance beyond the cricothyroid membrane. The guide then is removed and a suction catheter is introduced immediately to remove any blood or secretions. The tube is secured in place by a silk thread inserted through each end of the split portion of the tube and tied around the patient's neck (Fig 2).

To maintain tube patency, 1 to 2 mL of isotonic saline is instilled, followed by suctioning. This procedure is performed routinely and as required. A 4-mm tube will accommodate a 10F catheter and is adequate in most cases. It may be necessary to replace the tube if the lumen becomes blocked with inspissated mucus. Decannulation is performed when the patient is able to clear secretions through the larynx without assistance.

RESULTS

A total of 36 patients underwent minicricothyrotomy. In all cases it was performed at the bedside with the patient under local anesthesia. There were 22 male and 14 female patients, with an age range of 12 to 80 years. The duration of cannulation ranged from 4 to 62 days, with an average of 12 days. Three patients died of unrelated causes while fitted with the cannula, and four required a second endotracheal intubation or tracheotomy because they needed mechanical ventilation. The other 29 patients were decannulated successfully. Of these, 28 were followed up for periods ranging from 3 months to 3.5 years (mean, 20 months). There were no postoperative complications such as stomal infection, bleeding, or subcutaneous emphysema. There were no instances of accidental decannulation. Following decannulation, closure of the fistulous tract occurred within 2 to 5 days in all patients. Subglottic stenosis did not occur in any of the patients; this was concluded on the basis of clinical judgment as well as radiographic examination of the subglottic area by lateral soft tissue radiographs of the neck taken 8 to 28 months (mean, 16 months) postoperatively in 24 patients.

DISCUSSION

Minicricothyrotomy is indicated for patients who need no mechanical ventilation but do need assistance in clearing their tracheobronchial airways of secretions. It provides a convenient means of obtaining direct and permanent access to the trachea for suction while preserving the capabilities of normal speech, deglutition, and respiration. It is simpler and less invasive than existing alternatives and allows improved cleansing efficiency together with greater comfort for the patient. In addition, normal breathing assures the conditioning of the inspired air prior to its arrival in the lungs. Because of the small cross section of tracheal lumen occupied by the cannula, there is no danger of respiratory obstruction even if the cannula becomes blocked. It may allow earlier endotracheal extubation if only suction of secretions is needed. The nursing care required is simple. It is important to emphasize that the object of the procedure is control of secretions, not mechanical ventilation. It should be used at an early stage before the retention of secretions causes severe respiratory complications.

There has been a reluctance in the past to use the cricothyroid route for intubation, mainly because of the high incidence of subsequent subglottic stenosis. Discussion of the indications, contraindications, and limitations of conventional cricothyrotomy using a tracheotomy cannula is beyond the scope of this article and may be found elsewhere.[1,2] Such discussion is, however, irrelevant to the method proposed here, because it was found that the minimal distance between the inferior border of the thyroid cartilage and the superior border of the cricoid cartilage, at the midline, is 0.5 cm (average, 0.9 cm)[3] — larger than the diameter of the cannula used for minicricothyrotomy. Also, the tube softens with the warmth of the body, adapting itself to the shape of the cricothyroid space, so that there is little risk of compression of the cricoid cartilage. Other authors have documented the successful use of a small-bore tube inserted into the trachea for purposes of suction,[4] oxygen delivery,[5] and jet ventilation.[6]

Tracheobronchial toilet via a small-bore cricothyroid cannula offers a therapeutic modality that appears to be superior in most instances to traditional methods. Its use in departments of intensive care, neurosurgery, thoracic surgery, and pulmonary medicine may greatly facilitate the management of patients with problems of sputum retention.

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MORPHOMETRIC ANALYSIS OF NORMAL HUMAN SPIRAL GANGLION CELLS

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A morphometric analysis of the human spiral ganglion was performed at an ultrastructural level. Cells of the basal, middle, and upper middle turns were evaluated by serial section. The following parameters were evaluated: myelinization, area, diameter, circumference, and degree of roundness of the cell body and nucleus; diameter of the axon and dendrite in their initial segments; and process configuration. Analysis of variance suggested there were at least two types of cell bodies within the human spiral ganglion, best delineated by the dimensions of the cell body and nucleus and the ratio of diameter of the initial segments of axonic and dendritic processes. Myelinization and degree of roundness were relatively unimportant differential parameters. Cluster (multivariate) analysis of the six most important differential parameters suggested the possibility of five subgroups among the groups of large and small cells. For the middle and upper middle turns, cluster analysis suggested that there may be as many as three groups of cells based on morphometric analysis. These results are discussed in relation to other morphologic and physiologic data in the mammalian spiral ganglion.

KEY WORDS — electron microscopy, morphometry, spiral ganglion.

INTRODUCTION

Based on morphologic criteria, at least two distinct varieties of cell types have been found in the mammalian spiral ganglion.[1-7] The most complete data, including neurophysiologic correlation with anatomic findings, exist in the cat. In this species, the two types of spiral ganglion cell bodies have been classified as type 1, constituting approximately 95% of all cells present in the spiral ganglion, and type 2, constituting the remainder of cells.[8] The type 1 cell body is generally larger and has a more spherical nucleus than that of the type 2 cell. In addition, in the cat the type 1 cell is myelinated, whereas the type 2 cell is unmyelinated.[8,9] As evaluated by the horseradish peroxidase technique[9] and by retrograde degeneration,[8] the type 1 cells appear to innervate exclusively inner hair cells of the organ of Corti, whereas the type 2 cells innervate exclusively outer hair cells, at least in the adult cat.[9]

However, several lines of evidence would suggest that this bimodal morphologic classification of cell types in the spiral ganglion may be oversimplified. In an early description of the spiral ganglion in the rat, two types of cells of similar diameter were distinguished on the basis of filamentous content, suggesting that there may be subtypes of the type 1 spiral ganglion cell.[10] In the cat, differences based on neurotubule content have been described among the large myelinated fibers.[11] On physiologic grounds, there is evidence that there may be distinct functional subtypes of cells innervating inner hair cells, that is, the type 1 ganglion cell.[12,13]

Although there has been a paucity of data available for the human spiral ganglion, there is increasing evidence in the human of exceptions to the morphologic criteria established for two types of spiral ganglion cells observed in other mammals: most spiral ganglion cells, both large and small, are unmyelinated[6,14]; there may be subtypes of large cells based on cell shape; among large cells there are both bipolar and pseudomonopolar varieties in the neonate and adult[9]; and one example of a multipolar cell has been described in the human.[15]

Because of the paucity of normative data on the human spiral ganglion and the demonstration of distinct morphologic differences in the spiral ganglion of humans as compared to other mammals,

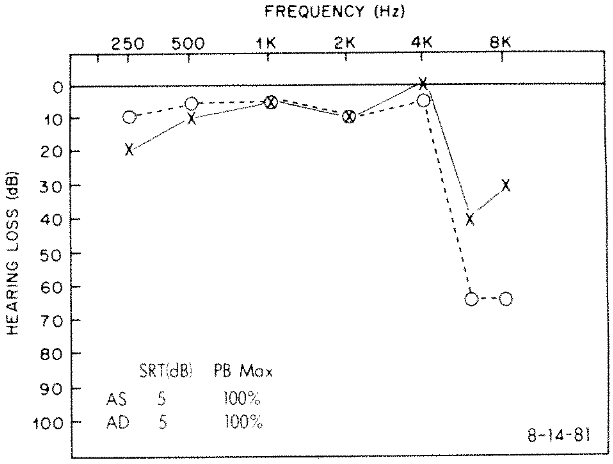

Fig 1. Audiogram of patient done 10 months before death.

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TABLE 1. MEAN VALUES OF MORPHOMETRIC PARAMETERS (±SD) AND ANALYSIS OF VARIANCE (ALL CELLS)

Parameter	*Basal Turn*	*Middle Turn*	*Upper Middle Turn*
Cell area (μm^2)	702.5±246.5	607.7±173.8	520.7±176.6
Cell diameter (μm)	30.5± 6.4	28.4± 4.8	26.5± 5.1
Cell circumference (μm)	97.6± 20.0	90.6± 15.0	84.2± 16.0
Cell roundness (%)	91.1± 6.2	90.5± 5.2	88.5± 7.7
Nuclear area (μm^2)	154.1± 36.6	111.1± 22.0	112.2± 26.0
Nuclear diameter (μm)	14.1± 1.9	11.9± 1.3	12.0± 1.5
Nuclear circumference (μm)	44.1± 6.0	37.7± 4.1	37.7± 4.7
Nuclear roundness (%)	98.7± 1.9	97.0± 1.7	97.5± 1.8
Axon diameter (μm)	3.7± 1.3	3.1± 0.7	3.2± 0.9
Dendritic diameter (μm)	1.4± 0.7	1.2± 0.3	1.3± 0.4

	Analysis of Variance	
Parameter	*Pairwise Comparison*	*p (Bonferroni)*
Cell area	Basal *v* middle	<.01
	Basal *v* upper middle	<.001
	Middle *v* upper middle	<.01
Cell diameter	Basal *v* middle	<.05
	Basal *v* upper middle	<.001
	Middle *v* upper middle	<.05
Cell circumference	Basal *v* middle	<.05
	Basal *v* upper middle	<.001
	Middle *v* upper middle	<.05
Cell roundness	Basal *v* middle	NS
	Basal *v* upper middle	<.01
	Middle *v* upper middle	NS
Nuclear area	Basal *v* middle	<.001
	Basal *v* upper middle	<.001
	Middle *v* upper middle	NS
Nuclear diameter	Basal *v* middle	<.001
	Basal *v* upper middle	<.001
	Middle *v* upper middle	NS
Nuclear circumference	Basal *v* middle	<.001
	Basal *v* upper middle	<.001
	Middle *v* upper middle	NS
Nuclear roundness	Basal *v* middle	<.001
	Basal *v* upper middle	<.001
	Middle *v* upper middle	NS
Axon diameter	Basal *v* middle	<.01
	Basal *v* upper middle	<.05
	Middle *v* upper middle	NS
Dendrite diameter	Basal *v* middle	<.05
	Basal *v* upper middle	NS
	Middle *v* upper middle	<.05

NS — not significant.

particularly at an ultrastructural level, this investigation was undertaken.

MATERIALS AND METHODS

Case History. A 21-year-old man died of osteogenic sarcoma of the left tibia, diagnosed 2 years prior to death. Medical treatment included an amputation and several courses of chemotherapy including methotrexate, Adriamycin, and cisplatin, which were completed by October 1981. Metastases to the lung and heart were diagnosed in May 1982, and he died June 1, 1982, without further treatment.

There was no history of hearing loss or vertigo. There was a history of noise exposure in the military and in his employment in a printing establishment. During the course of his chemotherapy, audiometry was performed. An audiogram done Aug 14, 1981, 10 months before death, is shown in Fig 1. This demonstrated normal hearing acuity below 4 kHz and a bilateral high frequency sensorineural loss. Speech discrimination was normal bilaterally.

Methods. Fixation of the inner ears was achieved 3.5 hours after death by perilymphatic perfusion with 2% glutaraldehyde and 2% paraformaldehyde in 0.1 *M* phosphate buffer at pH 7.2 via the oval and round windows. The temporal bones were removed subsequently at necropsy and immersed in the same fixative overnight. The mastoid air cell system was removed with rongeurs, and the otic capsule was thinned with a power drill before decalcification in 0.1 *M* disodium ethylenediaminetetraacetic acid (EDTA) with 2% glutaraldehyde in 0.1 *M* phosphate buffer.[16]

After decalcification, the cochlea was bisected and the turns were separated. The cochlea and spi-

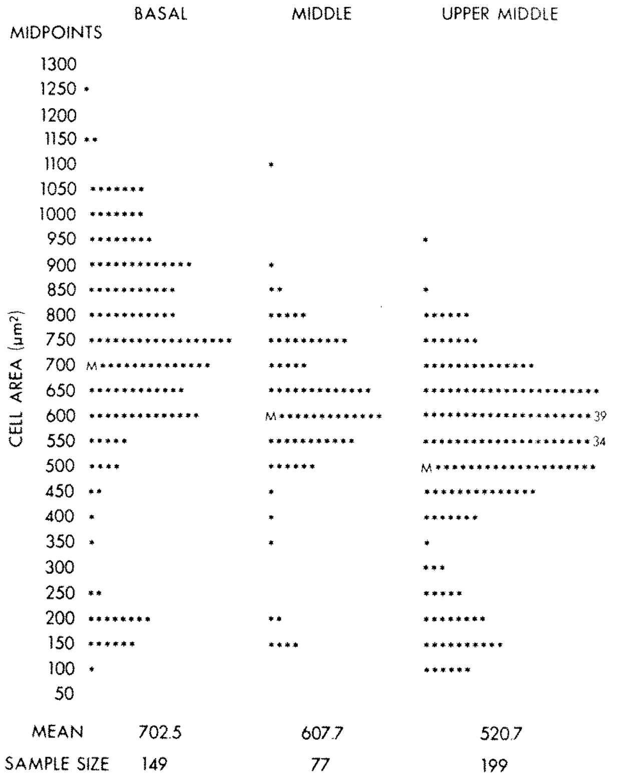

Fig 2. Histogram demonstrating distribution of all cells by cell area in basal, middle, and upper middle turns. Bimodal distribution is evident.

ral ganglion were divided into 1- to 2-mm segments, rinsed in buffer, and postfixed in 2% osmium tetroxide in 0.1 *M* phosphate buffer. The tissue was stained en bloc with aqueous uranyl acetate, dehydrated in graded alcohols, exchanged with propylene oxide, and embedded in Epon resin. Thick sections were stained with 1% toluidine blue O, and thin sections were stained with lead citrate.

Examination of the cochlea and spiral segments of both ears by light microscopy revealed a 10% to 20% loss of spiral ganglion cells limited to the basal 5 mm of the cochlea. There was a very slight loss of outer hair cells only in the basal 5 mm.

The following segments of the spiral ganglion were selected for further study by electron microscopy and serial section.

1. Segment 1B1, designated basal, was 5 to 7 mm from the basal end of the cochlea.
2. Segment 1M, designated middle, was 19 to 21 mm from the basal end of the cochlea.
3. Segment 3M, designated upper middle, was 26 to 28 mm from the basal end of the cochlea.

For each segment of the spiral ganglion, serial thin sections were taken in the radial direction, and every tenth section was photographed in its entirety to create an electron microscopic montage of the spiral ganglion at a magnification of 3,450x. Each cell was designated by number and followed through the serial sections. Only those cells for which the maximum cross-sectional diameter was present in the serial sections were included in the data base. This resulted in data on 149 cells in the basal turn, 77 cells in the middle turn, and 199 cells in the upper middle turn. The following parameters were evaluated:

1. Presence or absence of myelinization of the cell body.
2. Area, diameter, circumference, and degree of roundness of the cell body as measured in the section with the maximum cell diameter.
3. Area, diameter, circumference, and degree of roundness of the nucleus as measured in the section with the maximum nuclear diameter.
4. Diameter of the axon and dendrite in their initial segments.
5. Process configuration, ie, bipolar, pseudomonopolar, or other.

The area and circumference of cells and nucleus were computed by use of the MOP-3 morphometric system (Carl Zeiss, Inc, Oberkochen, Federal Republic of Germany). The degree of roundness of the cell body or nucleus was computed as a ratio of

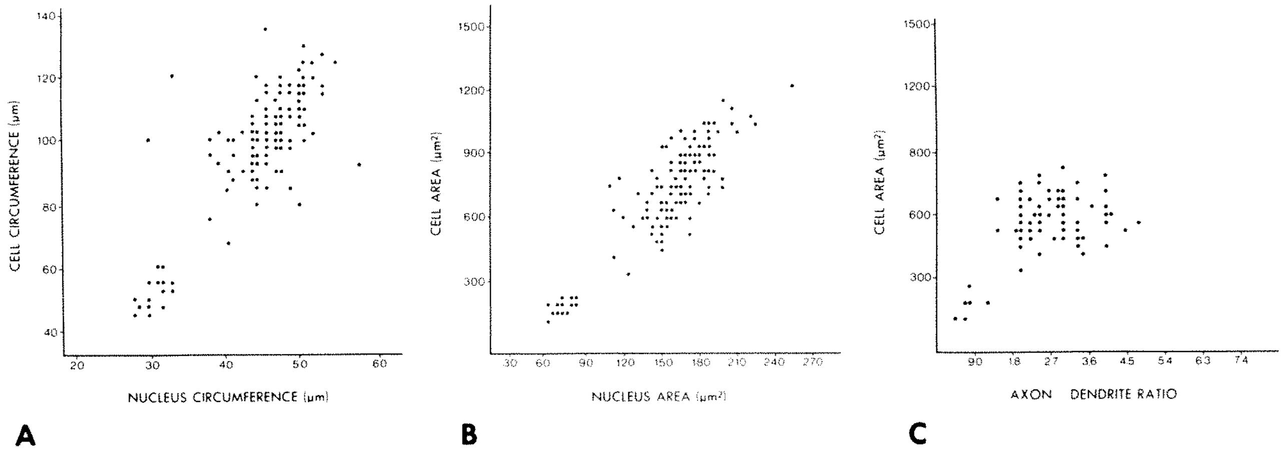

Fig 3. Bivariate scatter plots of parametric data in human spiral ganglion cells using A) cell and nuclear circumference, B) cell and nuclear area, and C) cell area and ratio of axonic and dendritic diameters.

TABLE 2. MEAN VALUES OF MORPHOMETRIC PARAMETERS (±SD) AND ANALYSIS OF VARIANCE (LARGE CELLS)

Parameter	*Basal Turn*	*Middle Turn*	*Upper Middle Turn*
Cell area (μm^2)	770.0±169.1	645.4±119.4	582.2±105.2
Cell diameter (μm)	32.4± 3.7	29.6± 2.8	28.4± 2.6
Cell circumference (μm)	103.5± 12.0	94.2± 8.8	90.1± 8.2
Nuclear area (μm^2)	164.7± 22.8	116.4± 14.0	121.7± 13.3
Nuclear diameter (μm)	14.5± 1.3	12.3± 0.7	12.5± 0.7
Nuclear circumference (μm)	45.2± 4.5	38.7± 2.3	39.4± 2.2

	Analysis of Variance	
Parameter	*Pairwise Comparison*	*p (Bonferroni)*
Cell area	Basal *v* middle	<.001
	Basal *v* upper middle	<.001
	Middle *v* upper middle	<.01
Cell diameter	Basal *v* middle	<.001
	Basal *v* upper middle	<.001
	Middle *v* upper middle	NS
Cell circumference	Basal *v* middle	<.001
	Basal *v* upper middle	<.001
	Middle *v* upper middle	<.05
Nuclear area	Basal *v* middle	<.001
	Basal *v* upper middle	<.001
	Middle *v* upper middle	NS
Nuclear diameter	Basal *v* middle	<.001
	Basal *v* upper middle	<.001
	Middle *v* upper middle	NS
Nuclear circumference	Basal *v* middle	<.001
	Basal *v* upper middle	<.001
	Middle *v* upper middle	NS

NS — not significant.

measured area divided by the area of a circle with the same diameter and expressed as a percentage.

Analysis of Data. The data were analyzed by analysis of variance, bivariate scatter plots, and cluster analysis.

RESULTS

Histograms and Analysis of Variance. For each segment of the spiral ganglion (basal, middle, upper middle), the mean and standard deviation of cell area, cell diameter, cell circumference, cell round-

TABLE 3. MEAN VALUES OF MORPHOMETRIC PARAMETERS (±SD) AND ANALYSIS OF VARIANCE (SMALL CELLS)

Parameter	*Basal Turn*	*Middle Turn*	*Upper Middle Turn*
Cell area (μm^2)	180.4±31.8	161.3±19.6	174.6±53.0
Cell diameter (μm)	15.8± 1.7	15.1± 1.2	16.3± 2.6
Cell circumference (μm)	52.1± 4.9	48.3± 4.0	52.0± 7.6
Nuclear area (μm^2)	71.9± 7.8	57.7±15.1	58.5± 9.5
Nuclear diameter (μm)	9.2± 0.4	8.3± 0.5	8.6± 0.6
Nuclear circumference (μm)	29.5± 1.1	26.0± 1.7	27.5± 1.8

	Analysis of Variance	
Parameter	*Pairwise Comparison*	*p (Bonferroni)*
Cell area	Basal *v* middle	NS
	Basal *v* upper middle	NS
	Middle *v* upper middle	NS
Cell diameter	Basal *v* middle	NS
	Basal *v* upper middle	NS
	Middle *v* upper middle	NS
Cell circumference	Basal *v* middle	NS
	Basal *v* upper middle	NS
	Middle *v* upper middle	NS
Nuclear area	Basal *v* middle	<.01
	Basal *v* upper middle	<.001
	Middle *v* upper middle	NS
Nuclear diameter	Basal *v* middle	<.01
	Basal *v* upper middle	<.01
	Middle *v* upper middle	NS
Nuclear circumference	Basal *v* middle	<.001
	Basal *v* upper middle	<.01
	Middle *v* upper middle	NS

NS — not significant.

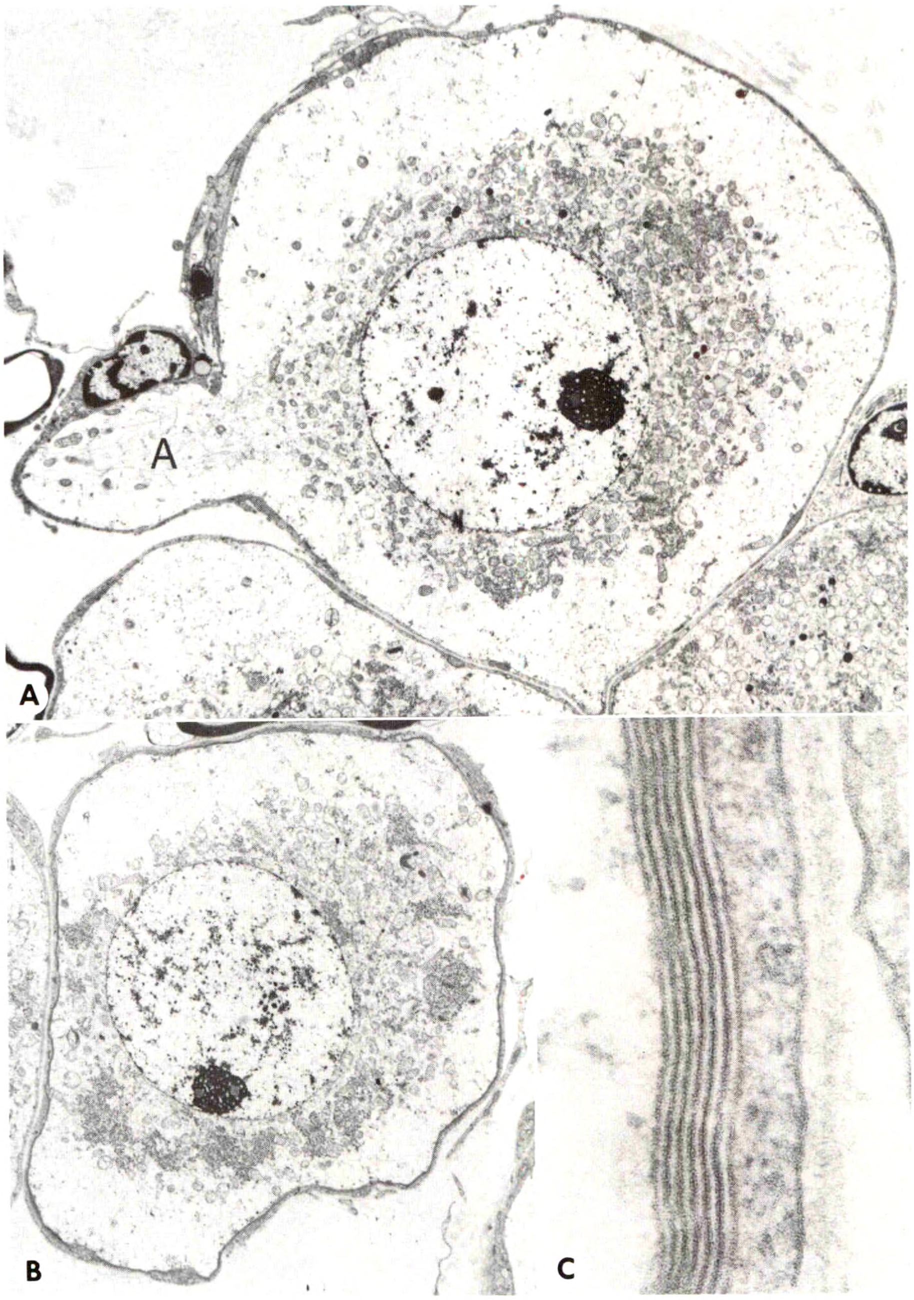

Fig 4. Large unmyelinated spiral ganglion cells in basal turn. A) At level of axon hillock (A) (original x2,650). B) Cell body at low magnification (original x2,650). C) Myelin lamellae of B at higher magnification (original x33,000).

ness, and nuclear area were calculated and a histogram of the distribution was computed. The mean values of this morphometric analysis and the analysis of variance for all cells are shown in Table 1, and a histogram for cell area is shown in Fig 2. For the parameters of cell area, cell diameter, and cell circumference, the calculated dimensions fit a bimodal distribution suggesting two types of cells: large and small (Fig 2).

The bivariate scatter plots also demonstrated two groups of cells for basal, middle, and upper middle turns. The parameters that best divided the cells into two groups were the areas and circumference of the cell body and nucleus and ratio of diameters of axon and dendrite (Fig 3). To calculate separately the mean dimensions and perform an analysis of variance for each of the two types of spiral ganglion cells, the entire population of cells was divided into two groups based on analysis of the histogram for each measured parameter. Cells were characterized as large if the cell area was ≥300 μm^2, cell diameter ≥21 μm, cell circumference ≥68 μm, nuclear area ≥90 μm, nuclear diameter ≥10 μm, and nuclear circumference ≥32 μm. Mean cell and nuclear parameters are presented for large cells in Table 2 and for small cells in Table 3. Typical examples of large and small cells are shown in Figs 4 and 5A,B.

Diameters of Cell Processes in Large and Small Ganglion Cells. The diameter of axonic processes of large cells was consistently larger than that of small cells in the basal, middle, and upper middle turns

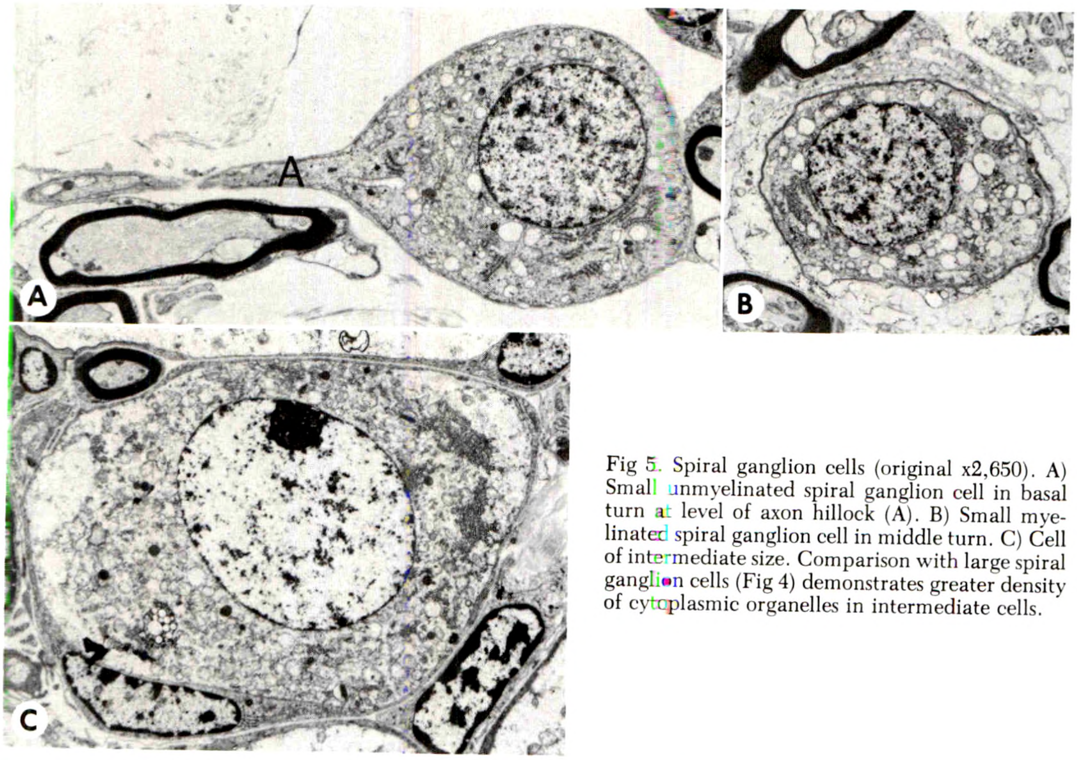

Fig 5. Spiral ganglion cells (original x2,650). A) Small unmyelinated spiral ganglion cell in basal turn at level of axon hillock (A). B) Small myelinated spiral ganglion cell in middle turn. C) Cell of intermediate size. Comparison with large spiral ganglion cells (Fig 4) demonstrates greater density of cytoplasmic organelles in intermediate cells.

(Table 4), whereas the mean diameter of dendritic processes was very similar among large and small cells in the three turns. The ratio of the diameter of the axon to that of the diameter of the dendrite varied between 2.8 and 3.2 μm for large cells and 0.8 to 2 μm for small cells in the three cochlear locations.

For large cells there were significant differences in the diameter of the axons among the three cochlear locations. Thus, the mean diameter of axons in the normal basal turn was significantly larger than that of the middle turn ($p<.001$, Bonferroni) and also that of the upper middle turn ($p<.01$, Bonferroni). The diameters of axons of the middle turn were not significantly different from those of the upper middle turn. The diameter of dendritic processes of large cells did not differ significantly in the three cochlear locations. Similarly, the ratio of axon diameter to dendrite diameter did not differ significantly for large cells in the three cochlear locations.

For small cells there were no significant differences in the diameters of axons in the three cochlear locations. There were insufficient data to analyze any differences in the diameter of dendrites or axon-dendritic ratio for small cells.

Myelinization. Most cell bodies in the basal, middle, and upper middle turns were unmyelinated. A few myelinated cell bodies were observed among both large and small cells (Table 5; Figs 4B,C and 5B).

Distribution of Large and Small Cells Across Three Sites of Spiral Ganglion. The percentage of small cells as determined by cell area, cell diameter, cell circumference, nuclear circumference, nuclear area, and nuclear diameter varied between 8% and 15% of all cells in the basal, middle, and upper middle turns. This difference was not significant for any parameter by the Pearson χ^2 analysis (Table 5).

Cluster Analysis. Cluster analysis is a multivariate statistical procedure that places objects into groups or clusters, considering all measured variables simultaneously. This was done to evaluate the possibility that groups of large and small cells, as determined by bivariate analysis, in actual fact contained subgroups. By use of the six variables of area, diameter, and degree of roundness of the cell body

TABLE 4. DIAMETERS OF CELL PROCESSES IN LARGE AND SMALL GANGLION CELLS

Turn	*Basal*		*Middle*		*Upper Middle*	
	Large	*Small*	*Large*	*Small*	*Large*	*Small*
Mean ± SD diameter of axon (μm)	4.0 ± 1.2	1.9 ± 1.2	3.2 ± 0.7	1.8 ± 0.3	3.5 ± 0.7	1.4 ± 0.6
n	91	10	54	3	126	16
Mean ± SD diameter of dendrite (μm)	1.4 ± 0.7	1.5 ± 0.6	1.2 ± 0.3	1.0	1.3 ± 0.4	1.5 ± 0.5
n	65	7	29	1	104	17
Ratio ± SD of diameter of axon to diameter of dendrite	3.2 ± 1.3	1.5 ± 0.8	3.0 ± 1.0	2.0	2.8 ± 0.7	0.8 ± 0.3
n	48	3	23	1	84	6

For large cells, cell area ≥ 300 μm^2. For small cells, cell area < 300 μm^2.

TABLE 5. INCIDENCE OF MYELINIZATION OF SPIRAL GANGLION CELLS BY TURN AND CELL SIZE

	Basal		*Middle*		*Upper Middle*		
	Large	*Small*	*Large*	*Small*	*Large*	*Small*	*Total*
Myelinated	8	0	0	1	8	0	17 (4%)
Unmyelinated	124	17	71	5	161	30	408
Total	132	17 (11%)	71	6 (8%)	169	30 (15%)	
Sample size	149		77		199		425

Large cells defined as cell area ≥ 300 μm^2.

and nucleus, cluster analysis was applied to spiral ganglion cells of the basal, middle, and upper middle turns. Graphic displays of the amount of variance accounted for by the number of clusters were generated for each variable. For normal basal cells (Fig 6A) the assumption of a five-cluster model accounted for 70% or more of the variance in each of the four variables of diameter and area of the cell body and diameter and area of the nucleus. Cluster centers and standard deviations for this five-cluster model are presented in Table 6. This Table indicates that there may be two types of large cells, both with mean areas of over 800 μm^2, one type of intermediate cell with a mean cell area of approximately 600 μm^2, and two types of small cells. An example of a cell of intermediate size is shown in Fig 5C. In addition to the difference in size, the cytoplasm of the intermediate cell is packed more densely with cell organelles, particularly mitochondria, than large cells (compare Fig 5C with Fig 4).

The same six variables were considered in cluster analysis of the cells of the normal middle and upper middle turns. The graphic reconstruction (Fig 6B,C) suggested that a three- or possibly two-cluster solution was appropriate for cells in these turns. Cluster means and standard deviations are shown in Table 7. Cells in the middle and upper middle turns seem to be divided into large, medium, and small groups.

DISCUSSION

Number of Cell Types Within Human Spiral Ganglion.

Analysis of variance and bivariate analysis suggested that there are at least two types of cell bodies within the human spiral ganglion in the basal, middle, and upper middle turns. The morphologic parameters that best delineated these two groups were the dimensions of the cell body and nucleus and the ratio of diameter of the initial segments of axonic and dendritic processes. As can be seen from the bivariate plots (Fig 3) and the data in Table 4, the ratio of diameter of axons versus dendrites in the initial segments varies from 0.8 to 2 μm for small cells and 2.8 to 3.2 μm for large cells. These data are in conformity with previously published data for spiral ganglion cells in other mammals.[9] The myelinization of cell bodies and degree of roundness of the cell and nucleus were not important differential parameters between large and small cells in the human, in contradistinction to the findings in the cat.[9]

Cluster (multivariate) analysis of the six most important differential parameters suggested the possibility of subgroups among the groups of large and small cells. In the basal turn, the solution to the cluster analysis suggested that there may be as many as five separate groups as determined by these morphometric parameters: two clusters of large cells, one cluster of intermediate cells, and two clusters of small cells. For the middle and upper middle turns, cluster analysis suggested that there may be as many as three groups of cells: large, intermediate, and small. The parameters of each of these putative clusters are displayed in Tables 6 and 7.

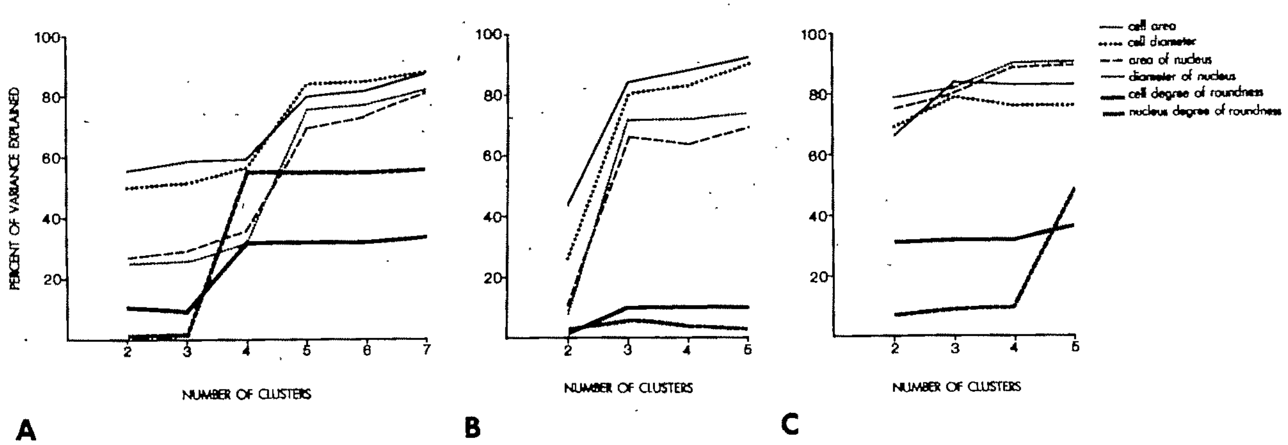

Fig 6. Percent of variance explained (R^2) in each of six variables by number of clusters for A) basal, B) middle, and C) upper middle turns. In basal turn, solution of five cell types or clusters is suggested by analysis. In middle and upper middle turns, analysis suggests two or three morphologic types of cells in spiral ganglion.

TABLE 6. CLUSTER MEANS (CENTERS) ± WITHIN-CLUSTER STANDARD DEVIATIONS FOR FIVE-CLUSTER MODEL (BASAL NORMAL CELLS)

Cluster	*No. of Cells*	*Cell Area* (μm^2)	*Cell Diameter* (μm)	*Cell Degree Roundness* (%)	*Nuclear Area* (μm^2)	*Nuclear Diameter* (μm)	*Nuclear Degree Roundness* (%)
1	56	816.3±122.2	33.4±2.62	92.3±4.31	173.9±22.5	15.0±0.88	99.0±1.16
2	39	589.2±90.2	28.6±2.62	89.9±5.41	154.7±16.3	14.3±0.85	98.9±1.28
3	37	889.8±138.2	35.0±2.75	92.8±5.41	161.4±24.2	14.5±1.19	98.8±1.21
4	3	177.3±46.5	15.8±2.84	68.3±10.69	70.7±7.8	9.7±0.51	89.0±2.65
5	14	181.1±30.2	15.8±1.50	89.9±5.65	72.2±8.0	9.5±0.62	98.9±1.59

The suggestion that there may be more than two subgroups of spiral ganglion cells is consistent with other morphologic and physiologic data. Thus, in an ultrastructural analysis of the spiral ganglion of the rat, Rosenbluth[10] has described two types of large ganglion cells, differentiated on the basis of cytoplasmic organelles and neurofilaments. In a correlation of physiologic and morphologic differences among radial afferent fibers in the cat, three functional groups based on the spontaneous discharge rate and threshold were described for a given region of characteristic frequency.[12,13] Since these physiologic differences all were measured from cell bodies innervating inner hair cells, these data would imply the presence of at least three functional subgroups of large spiral ganglion cells. Because the morphometric data obtained in the present study of the human spiral ganglion cell do not include information concerning the peripheral termination of these cells, no exact correlation with the cat data can be made.

Variation in Cell Size With Cochlear Location. As shown in Tables 1 and 2, the morphometric parameters of cell size were significantly different on the basis of cochlear location. Thus the mean area of the cell body for all cells (Table 1) and for large cells (Table 2) was largest among spiral ganglion cells in the basal turn, intermediate for cells in the middle turn, and smallest for cells in the upper middle turn. The difference in the area of the spiral ganglion cell has been observed also in the cat among cells with different characteristic frequencies.[13] In general, the cell bodies decreased in size in the range of characteristic frequencies from 0.16 to 3 kHz and then increased slightly in size from 3 to 40 kHz. These data suggested that the size of the cell body was related directly to the distance traversed by the spiral ganglion cell between the hair cells and the cochlear nucleus.

TABLE 7. CLUSTER MEANS (CENTERS) ± WITHIN-CLUSTER STANDARD DEVIATIONS FOR THREE-CLUSTER MODEL (MIDDLE NORMAL AND UPPER MIDDLE NORMAL CELLS)

Cluster	*No. of Cells*	*Cell Area* (μm^2)	*Cell Diameter* (μm)	*Cell Degree Roundness* (%)	*Nuclear Area* (μm^2)	*Nuclear Diameter* (μm)	*Nuclear Degree Roundness* (%)
Middle normal cells							
1	29	754.8±89.5	31.7±2.39	91.0±3.69	121.5±12.5	12.5±0.65	97.4±1.94
2	41	570.6±68.2	28.1±1.99	90.8±4.87	112.6±14.2	12.1±0.73	96.8±1.55
3	6	161.3±19.6	15.2±1.24	85.0±10.33	52.5±6.8	8.3±0.53	96.3±1.63
Upper middle normal cells							
1	62	682.9±76.2	30.4±2.12	90.7±5.51	128.5±11.4	12.9±0.62	97.5±1.40
2	28	171.4±54.2	16.2±3.01	77.8±11.46	57.3±8.4	8.6±0.56	96.3±3.41
3	108	521.2±74.4	27.0±2.31	90.0±5.01	117.4±13.1	12.3±0.68	97.8±1.24

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IMMUNOHISTOLOGIC FINDINGS IN OTOSCLEROSIS

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The cause of otosclerosis is still unclear. Between 1981 and 1988 we obtained 186 biopsy specimens of otosclerotic bone during the course of stapedectomies. Serial sections of the specimens were examined histologically (H & E) and immunohistologically (peroxidase-antiperoxidase technique) for immunoglobulin G, immunoglobulin M, and C1q and C3 complements. Active otosclerotic foci were found in 61 cases, 43 of which had IgG deposits. IgM antibodies were absent. In specimens with inactive otosclerosis, IgG and IgM were not evident. C1q and C3 complements were demonstrated together with IgG, but sometimes also in the mucosa independent of the phase of the otosclerosis. Our findings suggest that an immunologic process may be important in the pathogenesis of otosclerosis.

KEY WORDS — complement, immunoglobulin, immunohistology, otosclerosis, otospongiosis.

The cause of otosclerosis is still unknown. Numerous histologic, enzyme-histochemical, and biochemical studies have not revealed the cause of otosclerotic lesions. Only a hereditary factor is certain.[1,2]

Otosclerosis might be an autoimmune disease.[3,4] One test of this hypothesis is to demonstrate a morphologic correlate with an immune reaction or immune response. Since lymphocytes are seldom seen in otosclerotic foci, we believe that the humoral rather than the cellular immune system plays a role in the pathogenesis of otosclerosis.[5]

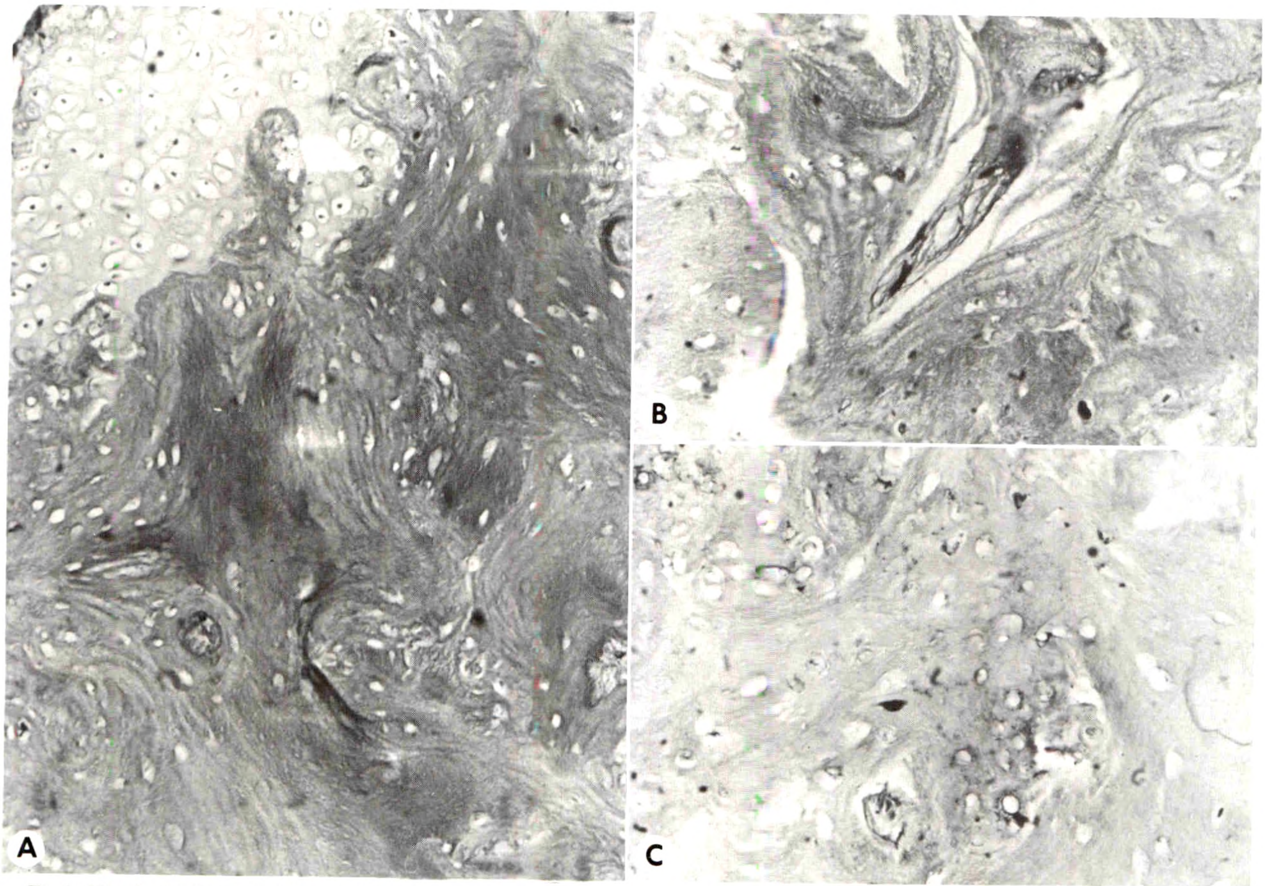

Fig 1. Histologically typical inactive otosclerotic foci. Neither immunoglobulin G nor immunoglobulin M antibodies found. A) H & E, original x100. B) Stained for IgG (peroxidase-antiperoxidase, original x250). C) Stained for IgM (PAP, original x250).

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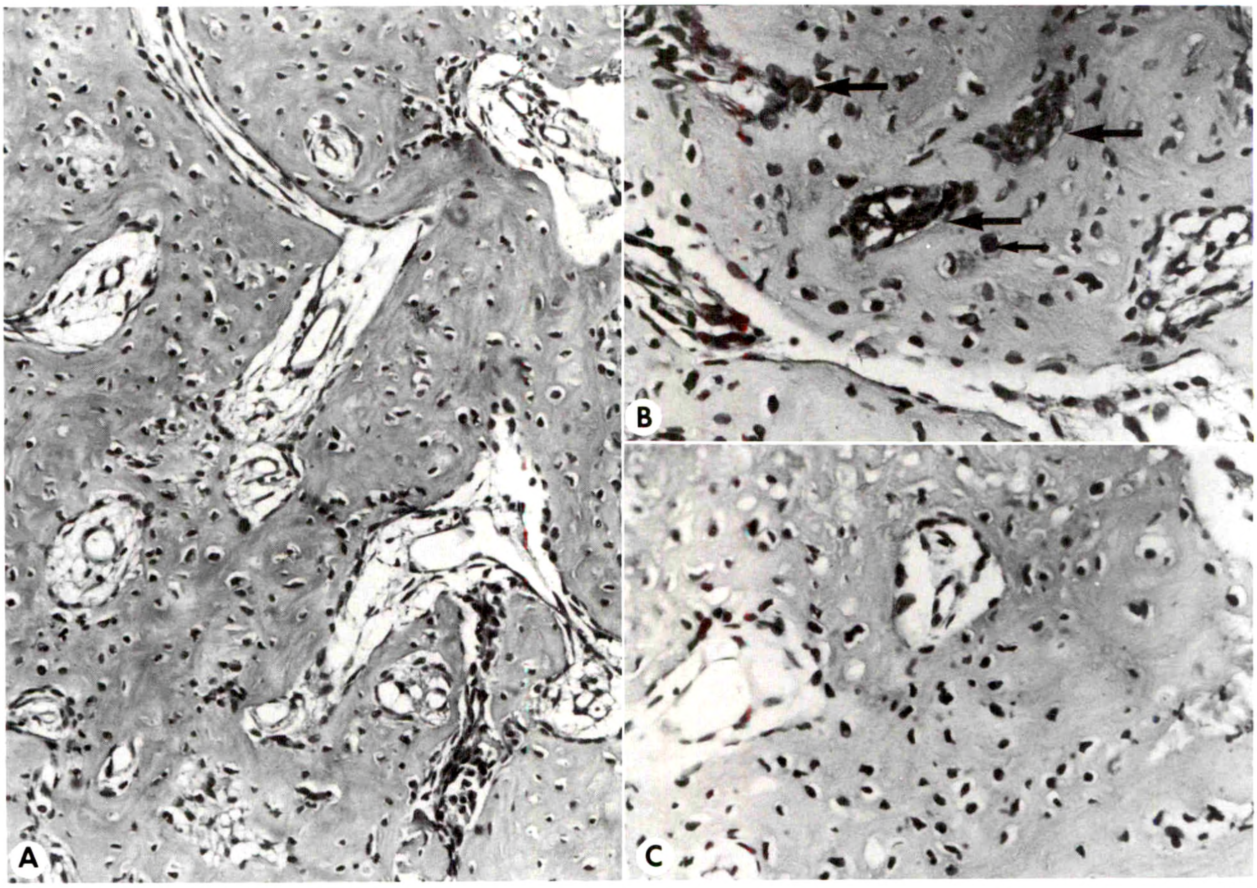

Fig 2. Active otosclerotic foci, showing enlarged marrow spaces, high cellularity, and irregular woven pattern of collagen fibrils. A) H & E, original x100. B) Stained for immunoglobulin G (peroxidase-antiperoxidase, original x250). Diaminobenzidine reaction is positive in histiocytes and especially in perivascular fibrous tissue. Arrows — brown-colored areas. C) Stained for immunoglobulin M (PAP, original x250). No IgM antibodies demonstrated.

MATERIAL AND METHODS

One hundred eighty-six biopsy specimens of otosclerotic lesions were taken during stapedectomy operations, 122 of them between 1981 and 1985. The majority of the specimens were from the posterior third of the footplate. The specimens were fixed in buffered formaldehyde (pH 7, 6%), decalcified (sodium edetate), and embedded with paraffin (below 60°C). Then 5-μm serial sections were cut and stained with hematoxylin and eosin or by the peroxidase-antiperoxidase (PAP) technique for immunoglobulin G and immunoglobulin M,[6] (immunoglobulins by DAKO, Copenhagen). A second series of 64 specimens (1986 to 1988) also was examined for C1q and C3 complements.

We differentiated histologically between active and inactive otosclerotic foci.[7-9] Our criteria of an active focus are high cellularity, increased vascularization, enlargement of the marrow spaces, lacunar resorption spaces with osteoclasts and osteoblasts, loss of bony ground substance, and an irregular woven pattern of the collagen fibrils, which is well demonstrated with polarized light.

RESULTS

According to the criteria mentioned above, we found purely inactive otosclerosis in 125 (67%; Fig 1) and active otosclerotic foci in 61 (33%; Fig 2) of our 186 specimens. The simultaneous occurrence of active foci within or beside inactive lesions is not uncommon. Examining sections of the same specimen after PAP staining revealed a positive reaction for IgG in 43 cases of histologically active otosclerosis (Fig 2B); thus, 70% of active foci are IgG positive. On the other hand, no IgG was evident in inactive otosclerosis (Fig 1B).

In the second series (64 cases) the incidence of C1q and C3 was concordant with IgG (Fig 3). However, there was a difference in the local distribution. While C3 was demonstrated in the perivascular space and at the monocytes within the otosclerotic focus (like the IgG), C1q was mainly demonstrating a positive reaction at the monocytes and less in the perivascular space. Both C1q and C3 complements also were seen in the mucosa and sometimes the submucosa (eg, Fig 3A). This latter finding appears in active otosclerosis, but also sometimes in inactive otosclerosis. IgM antibodies were not found in either the inactive or active otosclerotic lesions (Figs 1C and 2C). The results are summarized in Tables 1 and 2.

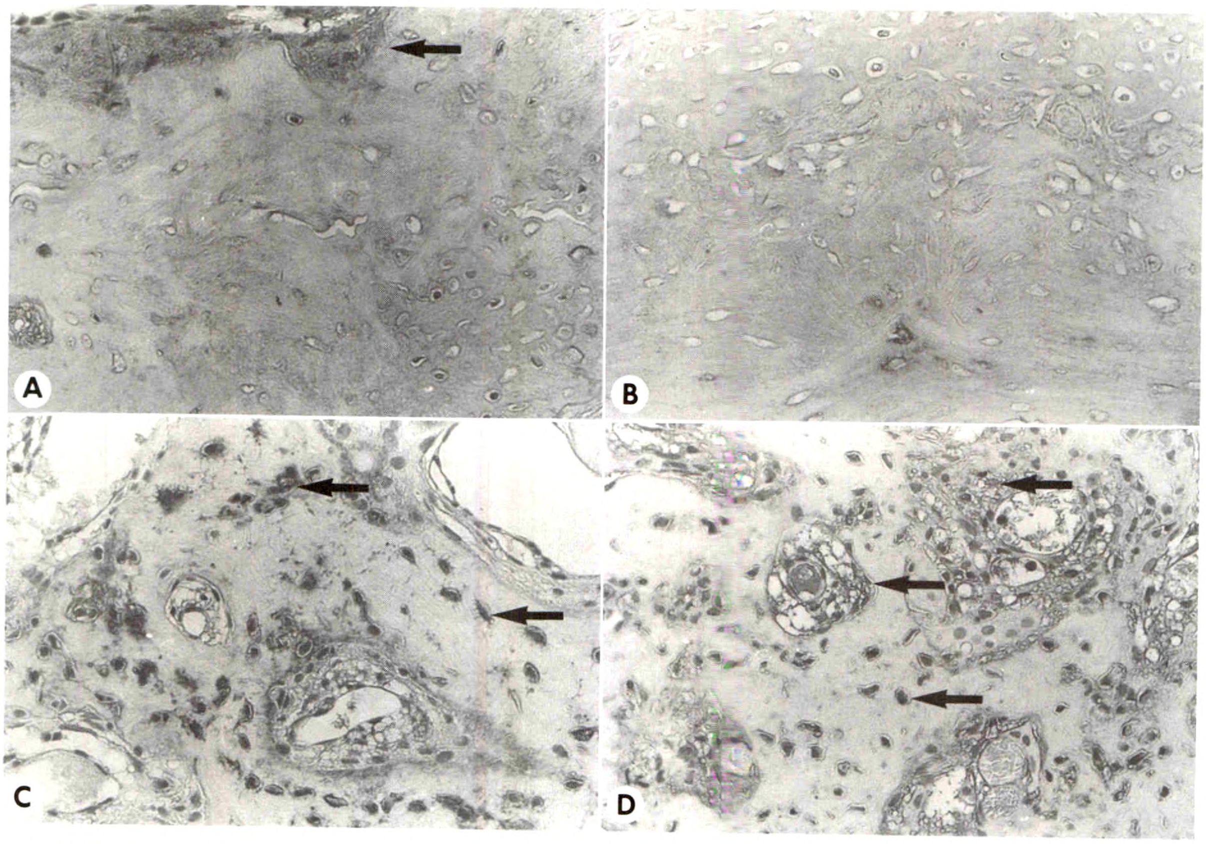

Fig 3. Otosclerotic foci stained for complements (original x250). Arrows — brown-colored areas. A) Inactive, stained for C1q (not found in this focus). Submucosa and mucosa seen, both demonstrating positive reaction for C1q. B) Inactive, stained for C3 (not found). C) Active, stained for C1q (found mainly in histiocytes, less in perivascular space). D) Active, stained for C3 (found in perivascular cells and also in single histiocytes).

DISCUSSION

The histogenesis of otosclerosis is quite clear.[10-12] The endochondral bone destruction is accompanied by a highly cellular fibrous tissue. It is supposed that mainly histiocytes[13] or altered osteocytes initiate the osteolytic phase by releasing hydrolytic enzymes.[14,15] Subsequently the intercellular ground substance leads to new bone production. By the repeating process of bone resorption and bone formation, a mosaiclike irregular woven pattern develops. The most frequent sites of involvement of the labyrinthine capsule are those with persisting embryonic cartilage.[10,16]

The proposed autoimmunologic cause of otosclerosis[3,17] has not yet been established. Contrary to Yoo et al,[18] Harris et al[19] did not find otoscleroticlike lesions after immunization of Wistar rats with bovine collagen II. Using the same method, Bretlau et al[20] found otoscleroticlike lesions in control — not immunized — rats as well. Therefore, the otoscleroticlike lesions found by Yoo et al[18] may be nonspecific spontaneous alterations rather than "immunologically" induced otosclerosis. A similar phenomenon has been described in LP/J mice.[21]

In contrast to Yoo et al, Harris et al, and Bretlau et al, we did not perform animal experiments, but examined human otosclerotic lesions obtained during stapedectomies. Seventy percent of the active otosclerotic foci showed IgG deposits. Since IgM was not demonstrable in active otosclerosis, a nonspecific 3.3 diaminobenzidine reaction with the fibrous tissue giving a false-positive result for IgG is rather unlikely. Also, a nonspecific occurrence of IgG next to the perivascular space simply by diffusion of the antibody across the endothelial layer is not probable. First, single cells then should not be

TABLE 1. CORRELATION BETWEEN ACTIVITY OF OTOSCLEROSIS AND IMMUNOHISTOLOGIC FINDING OF IMMUNOGLOBULIN G

	Active Otosclerosis	*Inactive Otosclerosis*	*Total*
IgG-positive	43	0	43
IgG-negative	18	125	143
Total samples	61	125	186

TABLE 2. CORRELATION BETWEEN C1Q AND C3 COMPLEMENT AND PHASE OF OTOSCLEROSIS

		Active Otosclerosis		
	Inactive Otosclerosis	*IgG-Positive*	*IgG-Negative*	*Total*
C1q-positive	0	15	0	15
C1q-negative	43	0	6	49
C3-positive	0	15	0	15
C3-negative	43	0	6	49
Total samples	43	21		64

IgG-positive, as they are (Fig 2B, small arrow). Second, the demonstration of C1q and C3 complements together with IgG emphasizes a specific reaction.

Therefore, we conclude that the active phase of otosclerosis is related to IgG fixation. It is possible that a humoral immune process stimulates the onset of otosclerosis, perhaps via stimulation of monocytes.

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QUANTITATIVE DISTRIBUTIONS OF ASPARTATE AMINOTRANSFERASE AND GLUTAMINASE ACTIVITIES IN THE GUINEA PIG COCHLEA

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Distributions of aspartate aminotransferase and glutaminase activities in the guinea pig cochlea have been examined with use of quantitative microchemical techniques to evaluate their roles in cochlear energy metabolism and neurotransmission. Other enzyme activities analyzed were those of choline acetyltransferase and malate dehydrogenase. It is concluded that aspartate aminotransferase activity appears to be especially concerned with cochlear energy metabolism, while glutaminase activity may function in transmitter metabolism in the guinea pig cochlea. Neither enzyme shows a clear association with the olivocochlear bundle.

KEY WORDS — aspartate aminotransferase, choline acetyltransferase, glutaminase, olivocochlear bundle, organ of Corti.

INTRODUCTION

Aspartate aminotransferase (AAT) (EC 2.6.1.1, L-aspartate:2-oxoglutarate aminotransferase), which exists as cytosolic (cAAT) and mitochondrial (mAAT) isoenzymes, catalyzes the amino group transfer from glutamate to oxaloacetate to form α-ketoglutarate and aspartate. This enzyme is essential in various cell metabolic pathways and may function in neurotransmitter metabolism of aspartatergic, glutamatergic, and/or γ-aminobutyratergic neurons.[1] Immunohistochemical staining methods have localized cAAT-like immunoreactivity to locations of olivocochlear fibers innervating outer hair cells (OHCs).[2]

Glutaminase (EC 3.5.1.2, L-glutamine aminohydrolase) catalyzes the hydrolysis of glutamine to glutamate and may be active in a glutamate cycle for production of transmitter in glutamatergic neurons.[1] Glutaminase-like immunoreactivity has been observed in areas of auditory nerve dendrites beneath inner hair cells (IHCs) and olivocochlear fibers and terminals beneath OHCs.[2]

In the cochlea, aspartate and glutamate have been considered putative neurotransmitters. Immunohistochemical and other methods have associated these amino acids with either the hair cell–auditory nerve system or the olivocochlear system, or both.[3] Both AAT and glutaminase are considered possible markers for neurons using these amino acids as transmitters.[1,4] Since both enzymes are involved in many cellular processes such as energy and ammonia metabolism,[5] it is difficult to associate them specifically with a function in neurotransmission as opposed to any other function.

The general purpose of this study was to use quantitative histochemical techniques,[6-8] which allow direct quantitative chemical measurements at microscopic resolution, to survey the relative distributions of AAT and glutaminase activities among six different cochlear substructures of the guinea pig. High enzyme activity in richly innervated regions, such as those containing IHCs and OHCs, may support the hypothesis that a particular enzyme is involved in neurotransmission. High activity in tissue with relatively little innervation, such as the stria vascularis, may suggest that an enzyme is concerned more with energy production. Malate dehydrogenase (MDH), an accepted marker for highly oxidative energy-producing tissues, was also studied.

A further purpose of the study was to evaluate the degree to which AAT and glutaminase activities are specifically associated with cholinergic olivocochlear fibers within the guinea pig cochlea, as suggested by immunocytochemical results.[2] This was done by comparing the distributions of AAT and glutaminase activities to that of choline acetyltransferase (ChAT) within the cochleas of control guinea pigs and in those that received transection of the olivocochlear bundle (OCB). The enzyme responsible for acetylcholine production in cholinergic neurons, ChAT exhibits a distribution of activity corresponding to that of olivocochlear fibers along the spiral organ of Corti, and disappears from the organ of Corti after OCB transection.[9]

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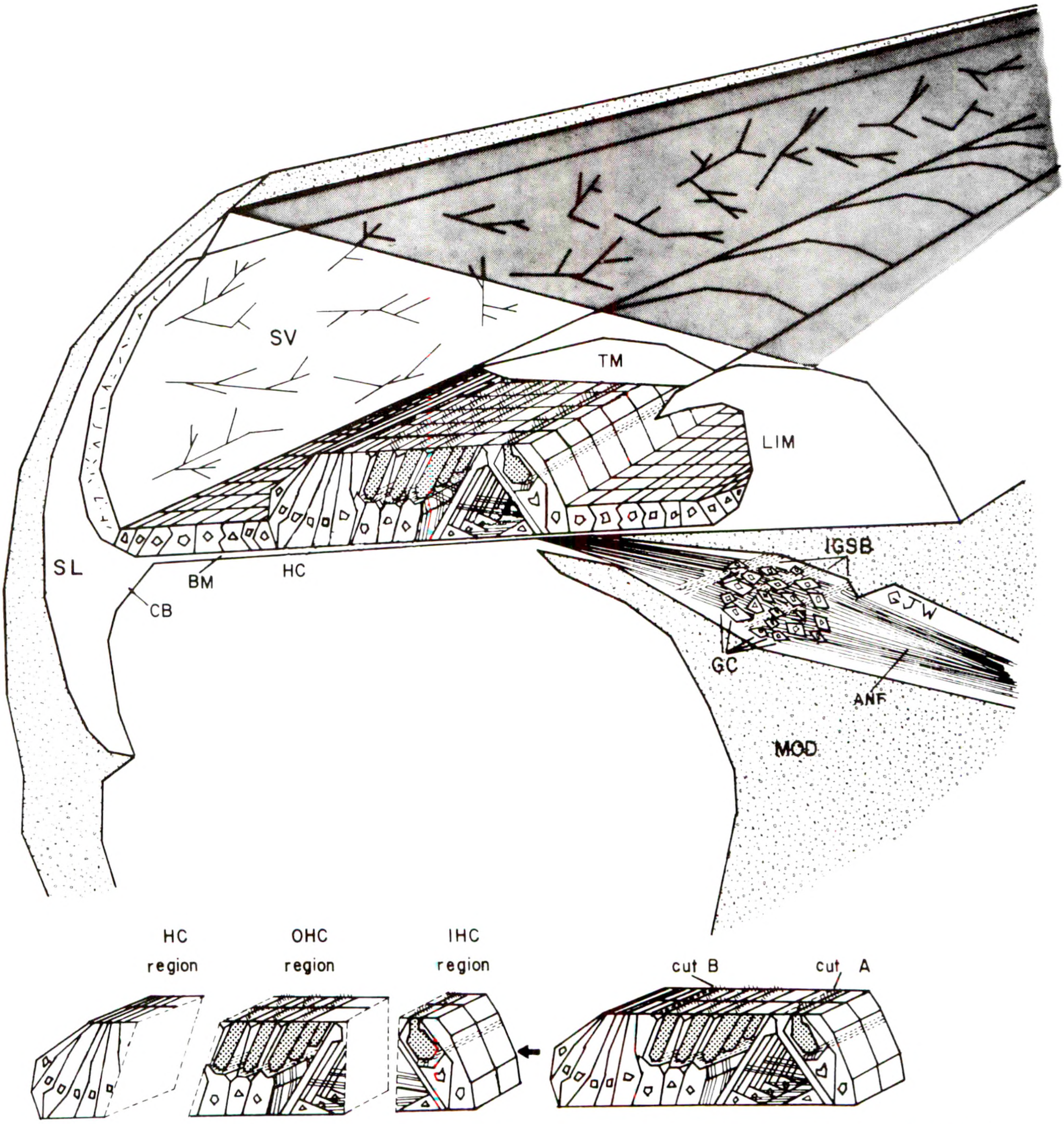

Fig 1. Schematic representation of cross section through middle turn of guinea pig cochlea demonstrating microdissection of organ of Corti regions. Lightly and regularly stippled regions — hair cells, lightly and irregularly stippled regions — bone, densely stippled region — Reissner's membrane, ANF — auditory nerve fibers, BM — basilar membrane, CB — crista basilaris, GC — ganglion cells, HC — Hensen's cells, IGSB — intraganglionic spiral bundle, IHC — inner hair cells, LIM — limbus, MOD — modiolus, OHC — outer hair cells, SL — spiral ligament, SV — stria vascularis, TM — tectorial membrane, cut A — separation of IHC region from OHC region, cut B — separation of OHC region from Hensen's cell region.

MATERIALS AND METHODS

Six male albino (Hartley) guinea pigs ranging in weight from 182 to 202 g and six male pigmented (English Shorthair) guinea pigs ranging in weight from 167 to 199 g were decapitated. The temporal bones of each animal were removed and prepared by methods similar to those previously described.[10] Isolated labyrinthine portions of temporal bones were frozen, usually 10 to 25 minutes postmortem, in Freon (Curtin-Matheson "Freeze-It") at its freezing-point temperature of $-130°C$. Additionally, nine NIH strain guinea pigs (pigmented) were studied in which lesions were made to destroy the vestibular portion of the left vestibulocochlear nerve, containing olivocochlear axons, just lateral to its point of emergence from the brain stem. The method of lesioning is described elsewhere.[11]

All cochleas were freeze-dried at $-40°C$ for 1 week and then were stored under vacuum at $-20°C$ until they were dissected under magnification (6x to 25x) by a three-dimensional approach facilitated by a small-mammal temporal bone holder.[10] Sections of spiral ligament including stria vascularis were cut, and samples of stria vascularis were separated along natural cell boundaries. Reissner's membrane was removed by hair point instruments, and the tectorial membrane was stripped from the organ of Corti with fine microforceps. Segments of organ of Corti were removed with microknives and further subdivided by separation of IHC regions (cut A, Fig 1), then OHC regions from Hensen's cell regions (cut B, Fig 1) at a magnification of 25x to 50x.[6,8-10] Samples for AAT, MDH, and glutaminase assays, weighed on quartz fiber microbalances,[7] ranged from 0.04 to 1.28 μg.

Two male Hartley albino and two male English Shorthair pigmented guinea pigs ranging in weight from 289 to 312 g were killed painlessly by decapitation, and their brains and cochleas were removed to make homogenates that were stored at −80°C. These homogenates were used for comparison of their enzyme activities with those of specific cochlear substructures. The cochlear homogenates were prepared in the same way as done previously for rats[10] (freezing took place 14 to 25 minutes postmortem) and assayed for protein concentration.[12] Homogenates were stored at −80°C until they were assayed. Enzyme activities for the homogenates were converted to the dry weight basis by multiplying values per wet weight (brain) by 4 or values per protein weight (cochlea) by 0.5.

Choline acetyltransferase activity was measured radiometrically by the same procedure as previously described.[10]

Total aspartate aminotransferase activity (tAAT) for five animals (three Hartley, two English Shorthair) and cytosolic (cAAT) activity (two Hartley animals) were determined by assays described elsewhere, based upon the production of a fluorescent pyridine nucleotide.[10] The average standard deviation across the series of tAAT assays was 4% of the mean for both the blank and the homogenate tubes. To assay preferentially for mitochondrial isoenzyme (mAAT) activity in three animals (two Hartley, one English Shorthair), the basic tAAT protocol was employed with 64 mmol/L KH_2PO_4 buffer, pH 6.0, instead of 60 mmol/L Tris buffer, pH 7.4, in the preincubation and an L-aspartate concentration of 2.5 mmol/L instead of 40 mmol/L in the incubation. This procedure is not as specific for mAAT as one established subsequently,[13] but strongly favors mAAT. No correction was made for the presence of a small amount of cytosolic activity or the absence of some mitochondrial activity under these conditions.

Glutaminase activity was measured in five animals (three Hartley, two English Shorthair) by a modification of the method described by Curthoys and Lowry[14] for phosphate-dependent glutaminase in the rat kidney. Across the series of assays, the average standard deviation for the blank tubes was about 4% of the mean, while for the homogenate tubes it was 15% of the mean.

Malate dehydrogenase activity was measured in two animals (one Hartley, one English Shorthair) as previously described.[15] The average standard deviation for the blank tubes across the series of assays was 1% of the mean, and for the homogenate tubes, 5% of the mean.

Differences between mean values of data were examined for statistical significance by a t test, with t expressed as the difference divided by the standard error of the difference and degrees of freedom as combined number of values in the two data sets minus 2.

RESULTS

The distributions of enzyme activities among cochlear substructures were similar for English Shorthair pigmented and Hartley albino guinea pigs (Fig 2), with interstrain correlation coefficients of 0.99, 0.96, 0.99, and 0.97 for tAAT, mAAT, MDH, and glutaminase activities, respectively. The activities of MDH, tAAT, mAAT, and cAAT were highest in the stria vascularis, and glutaminase activity, although low for all structures, was highest in IHC and OHC regions.

Activities of enzymes in the cochlear homogenates, as in the freeze-dried samples, were similar for the English Shorthair and Hartley guinea pigs. Means ± standard error of the mean for the eight cochlear homogenates were tAAT 10.4±0.7, cAAT 4.0±0.3, and glutaminase 0.1±0.01 mol/kg dry weight per hour. The glutaminase activity was strikingly low compared to the average for the brain homogenates from the same four guinea pigs: 5.7±0.1 mol/kg dry weight per hour.

No consistently significant basal-apical gradient of activity was demonstrated for any of the enzymes MDH, tAAT, mAAT, or glutaminase. This contrasts with ChAT activity, which, as previously demonstrated in guinea pigs,[16] has a prominent decrease apically in both IHC and OHC regions.

Four of the lesioned NIH strain guinea pigs were not included in the study because, during preliminary dissection, no recognizable organ of Corti structures were identified along the modiolus within the cochlea on the lesioned side. In three of the remaining animals, there was no significant difference in ChAT activity between lesion and control sides; this suggests that on the basis of previous results,[9,10] the operative procedure in these cases failed to produce transection of OCB. In two animals surviving 2 weeks and 3 weeks, ChAT activity was extremely low or undetectable in all samples of

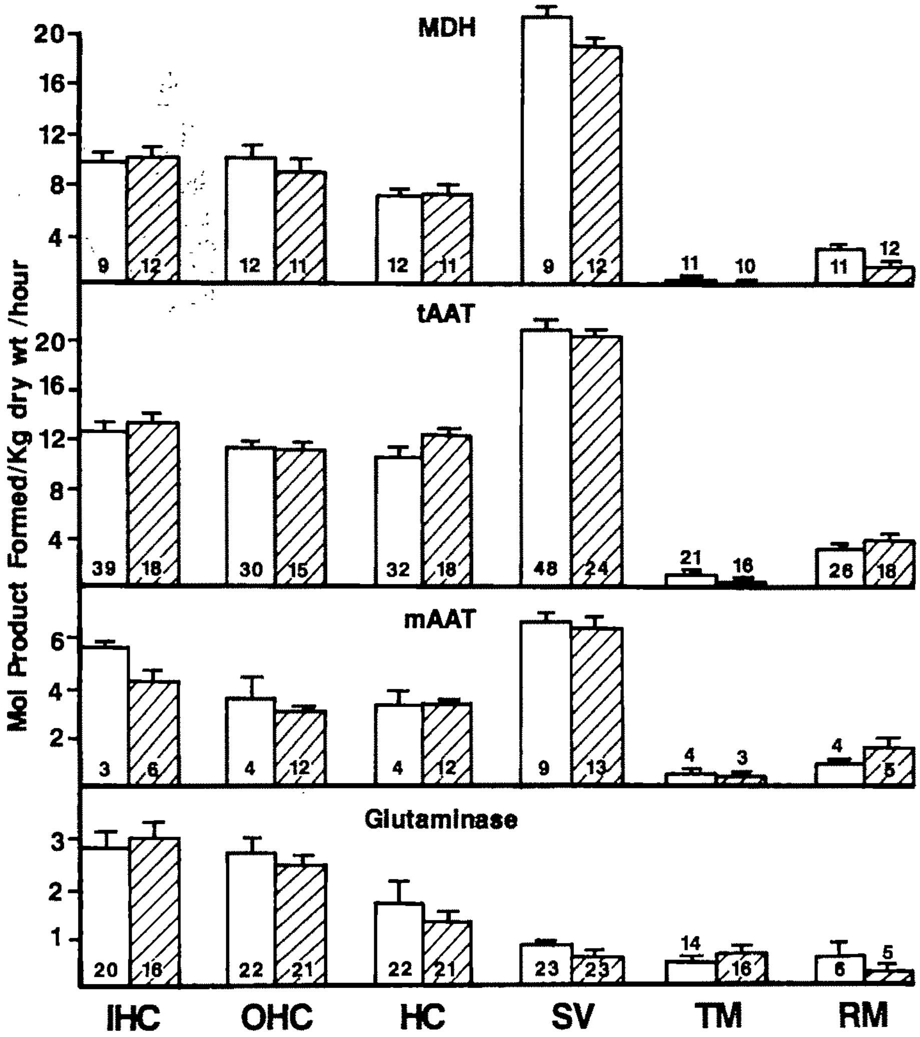

Fig 2. Means and standard errors of enzyme activities of Hartley albino (white bars) and English Shorthair (striped bars) guinea pig cochlear regions. Numbers on bars are numbers of samples. Numbers of animals are one Hartley and one English Shorthair for malate dehydrogenase (MDH), three Hartley and two English Shorthair for total aspartate aminotransferase activity (tAAT), two Hartley and one English Shorthair for mitochondrial aspartate aminotransferase (mAAT), and three Hartley and two English Shorthair for glutaminase. Only statistically significant differences between strains, at $p < .05$, were for mAAT in inner hair cell region (IHC) and MDH in stria vascularis. HC — Hensen's cell region, OHC — outer hair cell region, RM — Reissner's membrane, SV — stria vascularis, TM — tectorial membrane.

lesion-side organ of Corti after operation, implying essentially complete cholinergic OCB fiber transection.[9,10] Total AAT activity exhibited statistically significant differences only in the 3-weeks-postoperative animal, but the effects were not specific to the hair cell regions of the organ of Corti, occurring also in the Hensen's cell region and the stria vascularis. Glutaminase activity measured for the 2-weeks- and 3-weeks-postoperative guinea pigs demonstrated no statistically significant lesion- and control-side difference in the individual animals, but combining the data to increase the sample number demonstrated a significant difference in the IHC region. The relatively low overall activity of glutaminase made small differences between lesion- and control-side substructures difficult to resolve.

DISCUSSION

English Shorthair pigmented guinea pigs and Hartley albino guinea pigs had similar absolute enzyme activities for all regions studied. In the rat,[10] pigmented and albino strains had identical relative distributions, but absolute activities were different between the two strains.

The MDH activity in the guinea pig cochlea has been measured as an indicator of the tricarboxylic acid cycle and thus aerobic metabolic potential.[8] Although the MDH data are from only two animals, the findings are similar to previous results[8] in that the average MDH activity for the organ of Corti was about 44% of that in the stria vascularis, compared to 39% in the earlier study.

On the basis of the results presented, it seems reasonable to conclude that the majority of AAT activity within the cochlea is concerned with aerobic energy metabolism. The stria vascularis is the major contributor of the total energy for sound transduction in the inner ear[17] and has the highest metabolic rate among cochlear tissues.[18] The AAT activity (of each isoenzyme as well as the total) was significantly higher in the stria vascularis than in any other tissue sampled. Additionally, there was a close correlation between the distributions of MDH and AAT activities (correlation coefficient = 0.98). This is consistent with the proposal that these enzymes may exist in complex with other Krebs cycle enzymes, to facilitate the shuttling of reducing equivalents across the mitochondrial membrane for the generation of high-energy phosphorylated compounds.[19,20] By contrast, there was not a close correlation between the distribution of AAT and those of either of its two putative neurotransmitter substrates, aspartate and glutamate. Unlike AAT activity, the concentrations of both glutamate and aspartate are highest in the organ of Corti, exceeding those in the stria vascularis by factors of about 3 and 6, respectively.[9] Also unlike AAT activity, aspartate concentration in the organ of Corti has been observed to decrease from base to apex.[9]

If AAT activity is exclusively localized to olivocochlear fibers innervating OHCs, AAT activity in the OHC region should exceed that in the IHC region and exhibit a pattern of distribution similar to that of ChAT activity, including a significant (fourfold) decline from turn 1 to turn 4.[16] Neither of these trends was observed. Furthermore, the lack of detectable change in tAAT activity in the guinea pig surviving 2 weeks after transection of the OCB would argue against any highly specific association between AAT activity and olivocochlear fibers. Since the significant decreases of AAT activity in the hair cell regions of the 3-weeks-postoperative animal were accompanied by decreases in the Hensen's cell region and the stria vascularis, they must be attributed to some effect of the operation in addition to OCB transection.

Glutaminase activity was highest in the hair cell regions of the organ of Corti, suggesting a role of this enzyme in the metabolism of the cells particular to these regions, notably the hair cells, auditory nerve fibers, and olivocochlear fibers. Previous studies have localized elements of glutamate metabolism to these same regions. Glutamine, the substrate of glutaminase, has preferential uptake into hair cells, especially those in inner regions, and into bundles of olivocochlear fibers.[21,22] Glutamate, the product of glutaminase activity, and aspartate[9] have distributions among cochlear substructures generally similar to that of glutaminase activity, with correlation coefficients of 0.87 and 0.92, respectively. However, there are some inconsistencies. The concentration of aspartate, as stated earlier, exists in a gradient decreasing from base to apex, whereas no gradient of glutaminase activity was found. Also, the levels of glutamate and aspartate tend to be higher in the outer than in the inner part of the organ of Corti,[9] whereas glutaminase activity tends to be higher in the inner part, in both the rat[19] and the guinea pig. Further, the concentration of glutamate in the organ of Corti is comparable to that in brain, whereas glutaminase activity is relatively low. Such differences are not necessarily irreconcilable, since glutaminase activity may be only one of several factors determining the glutamate concentration in the cochlea. The low activities of glutaminase in cochlear substructures except the organ of Corti suggest that unlike AAT, glutaminase does not play a major role in nontransmitter metabolism. This is in contrast to the role that both AAT and glutaminase have in the retina.[15]

The results of this study argue against a specific association of glutaminase with olivocochlear fibers to OHC regions: no gradient of glutaminase activity was observed along the cochlear spiral, glutaminase activity was not higher in the OHC regions than in the IHC regions, and transection of the OCB, if anything, affected the IHC region glutaminase activity more than that of the OHC region. Alternatively, the glutaminase activity might be especially associated with peripheral processes of spiral ganglion cells that are transneuronally affected in the IHC region following OCB ablation.[23,24]

Olivocochlear bundle transection in the guinea pig had little selective effect on AAT or glutaminase activity in the OHC region. Although the results obtained for the guinea pigs with OCB transection were not as complete as those obtained previously for rats,[10] the similarity of the findings argues for the correctness of the overall results. Such a finding is inconsistent with the results from immunohistochemical labeling studies, wherein the antibodies against both enzymes showed quite specific labeling of the olivocochlear fibers innervating OHCs, correlating well with labeling for ChAT.[2,25] Since olivocochlear fibers occupy only a small portion of the organ of Corti,[9,10] changes in AAT and glutaminase activities within these fibers after OCB transection may be masked by the unchanged activities in the large volume of surrounding tissue. Further, these enzymes in the surrounding tissue may not react sufficiently with tagged antibodies to be noticeable in stained tissue sections. Alternatively, the antibodies in the immunohistochemical studies may be reacting with molecules in the olivocochlear fibers like, but different from, AAT and glutaminase.[25]

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MIDDLE EAR MUCOSA IN RAMSAY HUNT SYNDROME

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We report two patients with Ramsay Hunt syndrome, together with histopathologic findings of the middle ear mucosa near the facial canal. An attempt was made to find specific antigens of varicella zoster virus (VZV) and herpes simplex virus (HSV) by an immunofluorescence method. Histopathologic examination revealed inflammation of the middle ear mucosa. Specific VZV antigens were demonstrated in the cytoplasm and nucleus of elliptically shaped cells and round cells, but no specific antigens of HSV were found. The findings suggest a pathogenetic relationship between VZV infection and inflammatory changes in the middle ear mucosa.

KEY WORDS — immunofluorescence method, middle ear mucosa, Ramsay Hunt syndrome, varicella zoster virus antigen.

In an effort to improve the prognosis of facial palsy in Ramsay Hunt syndrome, Yanagihara et al[1] performed a decompression operation on the facial nerve in selected patients who showed signs of advanced denervation. During the operation, swelling or edema of the mucosa surrounding the geniculate ganglion or horizontal portion of the facial canal frequently was observed under an operating microscope.

There have been few reports of histopathologic findings of the middle ear mucosa in Ramsay Hunt syndrome. After a review of the literature, it appears unknown whether the swelling of the mucosa is caused by infection by the varicella zoster virus (VZV).

We report two patients with Ramsay Hunt syndrome, together with histopathologic findings of the middle ear mucosa. We focused attention on the specific antigen of VZV in the middle ear mucosa as revealed by an immunofluorescence method.

CASE REPORTS

Case 1. A 55-year-old woman complaining of total facial palsy and hearing loss on her right side consulted our department on Dec 25, 1986. Seven days before, she first felt a sharp pain in the right retroauricular area. On the same day, she became dizzy, and deafness of the involved ear occurred. These episodes were followed by hoarseness, dysphagia, and right facial palsy during the ensuing several days. After she was admitted on December 26, extensive medical treatments immediately were initiated after Ramsay Hunt syndrome with cranial polyneuropathy was diagnosed.

The patient's clinical examination revealed the following findings on the right side: vesicles and hyperemia of the eardrum, redness of the auricular and retroauricular skin, impairments in gag reflex, paralysis of the soft palate, and recurrent nerve paralysis.

Her hearing was almost totally impaired, as shown in the audiogram (Fig 1A). A Békésy audiogram showed a Jerger type II. The facial paralysis score was 6/40 points, an 85% paralysis, according to the scoring method of Yanagihara.[2] Although electrodiagnostic tests including a nerve excitability test and electroneuronography revealed no denervation of the facial nerve on the first visit, the denervation advanced to a total degree in the following 3 days.

Despite medical treatment including intravenous infusions of vidarabine (Ara-A) and gamma globulin, the facial palsy and other neurologic symptoms did not improve. A facial nerve decompression was performed 29 days after the onset of disease.

A transmastoid total decompression of the facial nerve revealed severe edema of the middle ear mucosa around the geniculate ganglion and horizontal portion of the facial nerve. The sheath of the facial nerve showed redness, and there was vascular dilatation limited to the horizontal portion and the geniculate ganglion. In the pyramidal portion, the sheath was very thick. The facial nerve was reddish and swollen, mainly in the horizontal portion. In the vertical portion, the sheath and the facial nerve appeared to be almost normal. Two specimens of the swollen mucosa in the vicinity of the geniculate ganglion and the horizontal portion were submitted to histopathologic and immunofluorescence examinations.

Case 2. A 9-year-old boy complaining of left facial palsy consulted our department on Dec 8, 1986, 6 days after the onset of disease. At the time of his first visit, there were erosion and crusts on the anterior skin of the left auricle. An otoscopic examination revealed no abnormality of the eardrum. Although he did not complain of any hearing disturbance, the audiogram (Fig 1B) indicated that he had a slight sensorineural hearing impairment on the affected side. The facial paralysis score was

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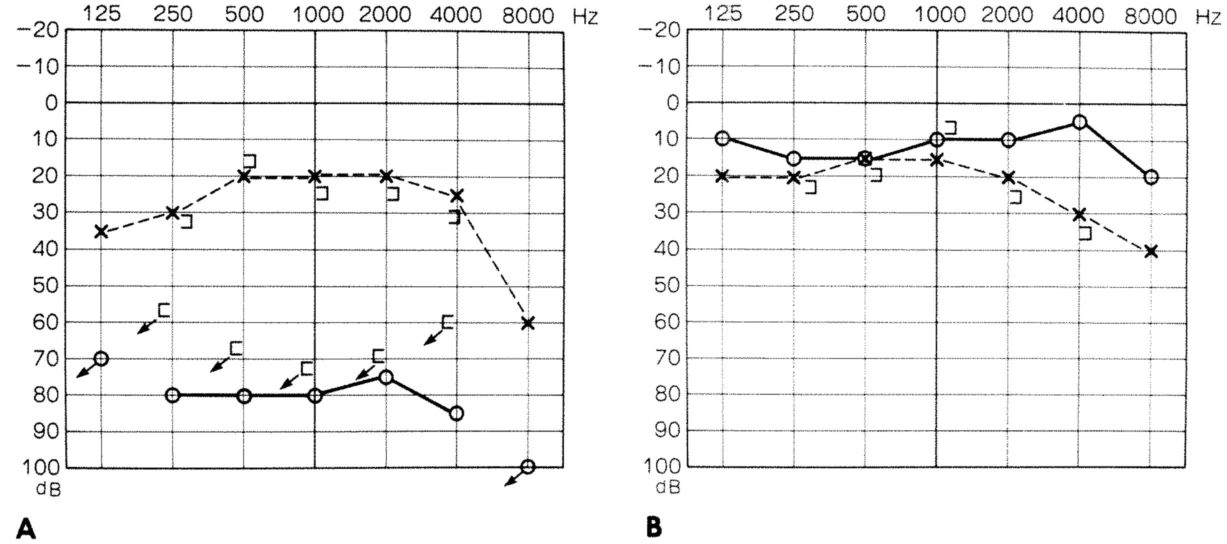

Fig 1. Audiograms of patients in study. A) Case 1. B) Case 2.

12/40 points, a 70% paralysis. There was no other neurologic disorder.

Electroneuronography showed a 92% denervation of the facial nerve. The facial palsy did not improve despite extensive medical treatment using vidarabine and prednisolone. Because of the high degree of denervation, a facial nerve decompression was performed 14 days after the onset of disease.

A transmastoid total decompression of the facial nerve revealed edema and redness of the middle ear mucosa close to the pyramidal eminence. The sheath of the facial nerve in the pyramidal portion showed severe redness.

The facial nerve had swollen diffusely from the geniculate ganglion to the vertical portion, and there was a pronounced edema noted in the horizontal portion. A piece of the swollen mucosa was taken from the pyramidal portion and submitted to histopathologic and immunofluorescence examinations.

HISTOPATHOLOGIC AND IMMUNOFLUORESCENCE EXAMINATIONS OF MIDDLE EAR MUCOSA

Histopathology. Immediately after resection, the specimens were fixed in 10% buffered formalin for 3 or 4 days and embedded in paraffin. For light microscopic observation, sections were stained with hematoxylin and eosin (H & E).

Immunofluorescence. An indirect immunofluorescence method was used to detect VZV antigen in the specimens. After formalin fixation, the specimens were embedded in paraffin and thin sections were made. After an appropriate enzymatic treatment using trypsin,[3] anti-VZV mouse monoclonal antibodies, antiglycoprotein and antinucleocapsid protein,[4] were applied to the sections overnight at 4°C. Then they were washed with phosphate-buffered saline (PBS). As the secondary overlay, anti-mouse IgG conjugated with fluorescein isothiocyanate (Miles-Yeda Ltd, Israel) was applied for 1 hour at 37°C. Again the sections were washed with PBS. Finally the sections were mounted with buffered glycerin (pH 9.2) and observed under a fluorescence microscope.

In addition to VZV, herpes simplex virus (HSV) type 1 antigen was also investigated with use of the indirect immunofluorescence method. The anti-HSV antibody was made in New Zealand white rabbits by infection with type 1 HSV (Tomioka strain). As the secondary overlay, anti-rabbit IgG conjugated with fluorescein isothiocyanate (Miles-Yeda Ltd) was applied.

Findings. Figure 2A,B shows photomicrographs of H & E staining in case 1. Figure 2A shows the findings of the biopsy of the mucosa near the geniculate ganglion. There was a pronounced inflammation in the interstitial portion of the mucosa. The infiltrating cells were mainly lymphocytes with scattered plasma cells. Figure 2B shows the findings of the biopsy of the mucosa near the horizontal portion of the facial nerve. There was a mild inflammation associated with degeneration and infiltration of small round cells. No intranuclear inclusion body was found (Fig 2A,B).

Figure 2C shows the findings of the immunofluorescence corresponding to Fig 2B. The specific immunofluorescence of VZV antigens in the cytoplasm and nucleus of elliptically shaped cells was clearly demonstrated. A similar finding of immunofluorescence was seen in the specimen shown in Fig 2A. No HSV antigen was found in either specimen.

Figure 2D is a photomicrograph of H & E staining of the mucosa in close vicinity to the pyramidal eminence in case 2. Under the preserved epithelial layer, infiltration of lymphocytes with scattered elliptically shaped cells was evident, together with weak fibrosis. As shown in Fig 2E, the specific im-

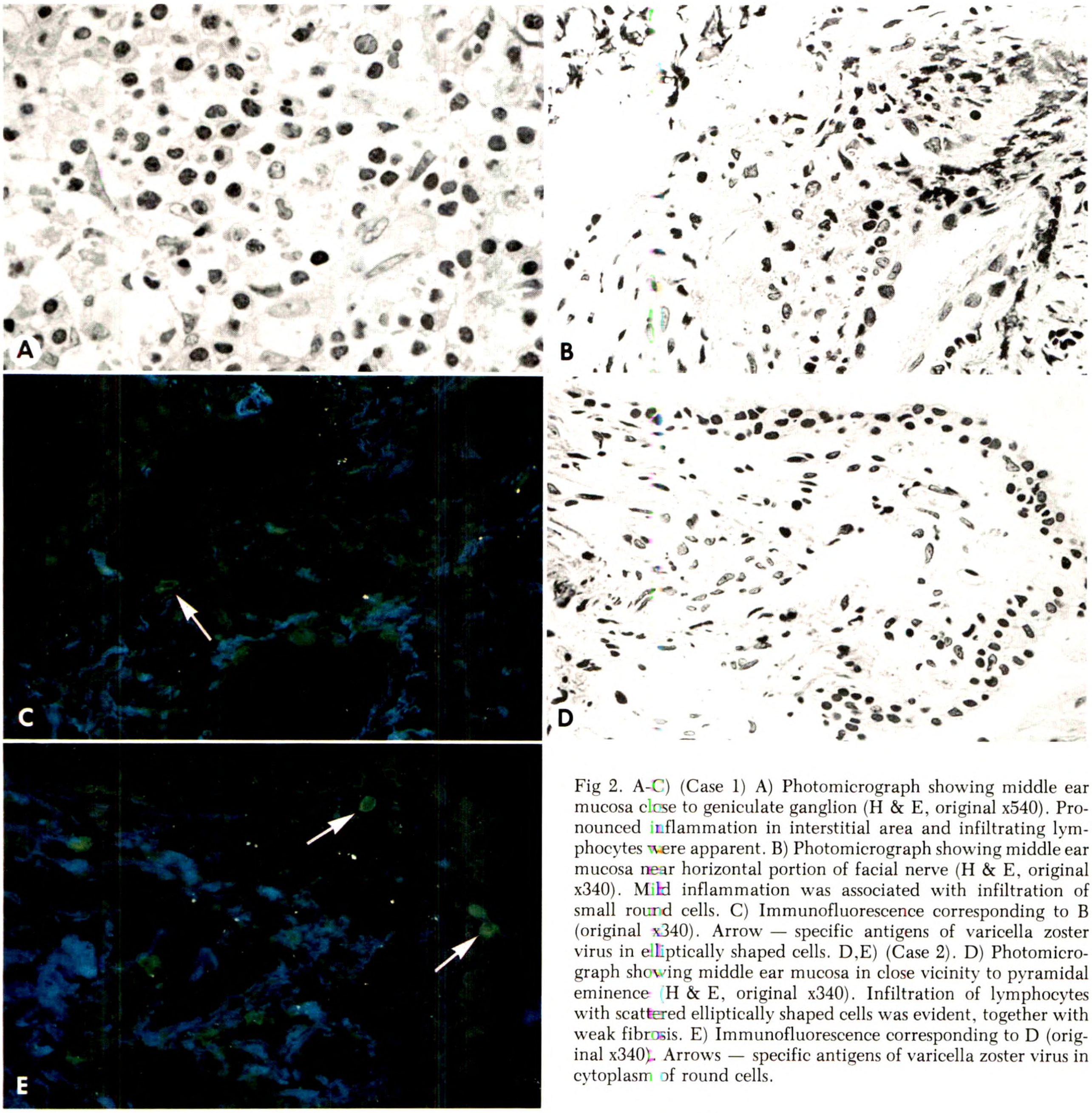

Fig 2. A-C) (Case 1) A) Photomicrograph showing middle ear mucosa close to geniculate ganglion (H & E, original x540). Pronounced inflammation in interstitial area and infiltrating lymphocytes were apparent. B) Photomicrograph showing middle ear mucosa near horizontal portion of facial nerve (H & E, original x340). Mild inflammation was associated with infiltration of small round cells. C) Immunofluorescence corresponding to B (original x340). Arrow — specific antigens of varicella zoster virus in elliptically shaped cells. D,E) (Case 2). D) Photomicrograph showing middle ear mucosa in close vicinity to pyramidal eminence (H & E, original x340). Infiltration of lymphocytes with scattered elliptically shaped cells was evident, together with weak fibrosis. E) Immunofluorescence corresponding to D (original x340). Arrows — specific antigens of varicella zoster virus in cytoplasm of round cells.

munofluorescence of VZV antigen was demonstrated in the cytoplasm of the scattered cells in the specimen shown in Fig 2D. No specific HSV antigen was demonstrated in this specimen.

DISCUSSION

Ramsay Hunt syndrome is caused by reactivation of VZV infection. Although a considerable number of autopsy and temporal bone studies on Ramsay Hunt syndrome have been reported,[5-11] histopathologic examinations of the middle ear mucosa in this disease are lacking. The main interest of all the investigators lies in the histopathologic findings of the facial nerve, other cranial nerves, and the inner ear. A consistent finding of previous postmortem studies on Ramsay Hunt syndrome was widespread lymphatic infiltration along the entire course of the facial nerve. It also has been accepted that other cranial nerves besides the facial nerve are frequently involved in this syndrome, as in case 1.

Only in the case reported by Blackley et al[10] have the histopathologic changes in the middle ear been described. Their case involved a 69-year-old woman who died of carbon monoxide poisoning 214 days from the onset of a herpetic eruption. Her middle ear was lined with normal epithelium, and in places, particularly near the facial nerve and at the reflection of the epithelium onto the ossicle, the submucosa was thickened with intense perivascular inflammation. The cells were mainly lymphocytes with occasional plasma cells, macrophages, and osteoclasts. In this paper, however, no further attention was paid to these findings. It is worthy of note that the above findings are very similar to those of the present case 2.

The present study, as well as the case reported by Blackley et al, has indicated that in the limited known cases of Ramsay Hunt syndrome, inflammatory changes have taken place in the middle ear mucosa close to the facial canal, from the geniculate ganglion to the pyramidal portion.

In order to know whether the inflammatory changes are caused by a viral infection, the indirect immunofluorescence method is thought to be appropriate as long as due care is taken to avoid technical failure. In order to avoid artifact causing misinterpretation of the result, a proper control study has to be done. Using the same method, we have examined specimens of middle ear mucosa taken from eight patients with Bell's palsy and two patients with traumatic facial palsy. In these specimens, no specific antigens of either VZV or HSV were demonstrated. We also have used the same immunofluorescence technique in extensive animal experiments in the HSV-inoculated mouse and established the reliability of the investigational method. Thus, the positive immunofluorescence in the present study indicates VZV antigens in the middle ear mucosa specimens of both patients.

In our specimens, VZV antigens were demonstrated mainly in the cytoplasm. The monoclonal antibodies used in this study can recognize principally glycoproteins or nucleocapsid proteins in the cytoplasm or nucleus, respectively, or both. Taking into account this property of the antibodies, it is not strange that the VZV antigens were preponderant in the cytoplasm. The finding can reasonably be attributed to the pathogenetic relationship between VZV infection and inflammatory changes of the middle ear mucosa.

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DIZZINESS MANAGEMENT CONFERENCE

The Department of Otolaryngology and Audiology Services, Medical College of Ohio, will host a Dizziness Management Conference on June 9, 1990. For further information, contact Randa Mansour-Shousher, MS, CCC-A, Audiology, Medical College of Ohio, 3000 Arlington Avenue, Toledo, OH 43614; (419) 381-4012.

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DISTRIBUTION OF ELASTIC CARTILAGE IN THE ARYTENOIDS AND ITS PHYSIOLOGIC SIGNIFICANCE

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An investigation of the distribution of the elastic cartilage in the arytenoids was performed on excised human adult and newborn larynges. The distribution of elastic cartilage in the arytenoids was investigated histologically in two serial sections: horizontal and coronal. The behavior of the elastic cartilage portion of the arytenoids was investigated histologically under the conditions of adduction and abduction. The results are summarized as follows. 1) Elastic cartilage is found not only at the tip of the vocal process but at the superior portion of the arytenoid cartilage from the vocal process to the apex. 2) This phenomenon is observed at birth. 3) The vocal process bends at the elastic cartilage portion during adduction and abduction. The sides of the arytenoids come into contact mainly at the elastic cartilage portion. 4) Elastic cartilage appears to play an important role in the physiologic functioning of the arytenoid.

KEY WORDS — arytenoid cartilage, elastic cartilage, larynx, vocal process.

INTRODUCTION

Among the laryngeal cartilages, only the arytenoid cartilage is composed of two types of cartilage, ie, elastic cartilage and hyaline cartilage. There is no general agreement on the distribution of elastic and hyaline cartilages in the arytenoid. These two types of cartilage have very different properties and so the distribution of the elastic and hyaline cartilages in the arytenoid and its possible functional significance are of interest.

In this paper, a detailed investigation of the distribution of the elastic cartilage in the arytenoid is reported, and its physiologic significance discussed.

MATERIALS AND METHODS

A total of 37 normal human larynges obtained from autopsy cases were used. Of the 37 larynges, 27 were from adults and ten were from newborns. Of the 27 adult larynges, ten were from men ranging from 44 to 75 years of age, and 17 were from women ranging from 37 to 81 years of age. Of the ten newborn larynges, five were from boys and five were from girls. All of them were mature newborns.

The adult laryngeal specimens were fixed in 10% formalin and embedded in paraffin under three conditions: 1) neutral condition, in which no force was applied to the arytenoid cartilage; 2) vocal fold adduction, in which the muscular processes of the bilateral arytenoid cartilages were pulled by threads in the direction of the combined forces of the lateral cricoarytenoid and thyroarytenoid muscles; and 3) vocal fold abduction, in which the muscular processes of the bilateral arytenoid cartilage were pulled by threads in the direction of the force of the posterior cricoarytenoid muscle.

The newborn laryngeal specimens were fixed in 10% formalin and embedded in paraffin under the neutral condition.

With these specimens, horizontal and coronal serial sections were made. Horizontal serial sections were made parallel to the membranous portion of the vocal fold. Coronal serial sections were made vertical to the membranous portion of the vocal fold.

Among the adult laryngeal specimens, horizontal serial sections were made from 18 larynges: ten in the neutral condition, four in vocal fold adduction, and four in vocal fold abduction. Coronal serial sections were made from nine larynges: six in the neutral condition, and three in vocal fold adduction. Among the newborn laryngeal specimens, horizontal serial sections were made from six larynges and coronal serial sections were made from four larynges.

Hematoxylin and eosin and elastica-van Gieson stains were employed for each section and then the sections were observed microscopically.

RESULTS

Distribution of Elastic and Hyaline Cartilage in Arytenoids of Adult Larynges. Figure 1A shows a horizontal section of the vocal process of an adult larynx. The posterior macula flava is observed at the posterior end of the membranous portion of the vocal fold. Posterior to it, there is the tip of the vocal process. The major part of the vocal process is composed of hyaline cartilage, whereas the tip is composed of elastic cartilage.

Figure 1B shows a higher magnification of the tip

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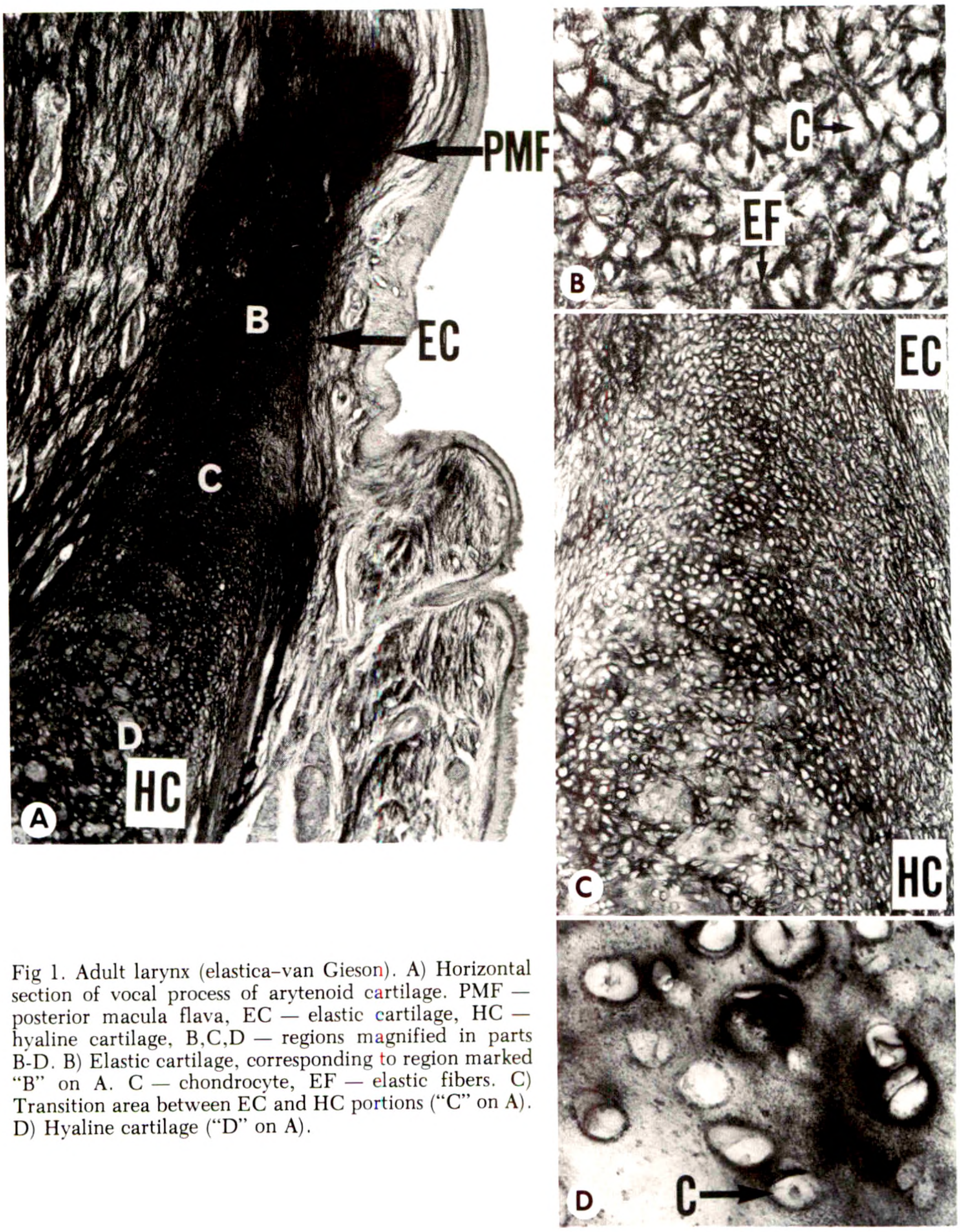

Fig 1. Adult larynx (elastica–van Gieson). A) Horizontal section of vocal process of arytenoid cartilage. PMF — posterior macula flava, EC — elastic cartilage, HC — hyaline cartilage, B,C,D — regions magnified in parts B-D. B) Elastic cartilage, corresponding to region marked "B" on A. C — chondrocyte, EF — elastic fibers. C) Transition area between EC and HC portions ("C" on A). D) Hyaline cartilage ("D" on A).

of the vocal process. The chondrocytes and ground substance (elastic fibers) reveal that the tip of the vocal process is composed of elastic cartilage. Figure 1C shows the transition area between the elastic and hyaline cartilage portions. The number of elastic fibers decreases toward the posterior level of the vocal process. More posteriorly, the chondrocytes and ground substance indicate that this portion is composed of hyaline cartilage (Fig 1D). The transition between the elastic cartilage portion and the hyaline cartilage portion is gradual, and the border between them is not clearly delineated.

Figure 2 shows coronal sections of the arytenoid cartilages of adult larynges. The tip of the vocal process is elliptic in shape and composed only of elastic cartilage (Fig 2A). As the sections are followed posteriorly, the superior portion of the arytenoid cartilage is composed of elastic cartilage and the inferior portion of it is composed of hyaline cartilage (Fig 2B-D). More posteriorly, only a small part of the apex is composed of elastic cartilage (Fig 2E). As was stated previously, the transition between elastic and hyaline cartilage portions is gradual, and the border between them is not clearly delineated.

In cases of arytenoid cartilage ossification, the hyaline cartilage portion ossifies, but the elastic cartilage portion does not ossify.

Distribution of Elastic and Hyaline Cartilage in Arytenoids of Newborn Larynges. Figure 3A shows a horizontal section of the vocal process of a newborn larynx. Posterior to the posterior macula flava there is the tip of the vocal process. Figure 3B shows a

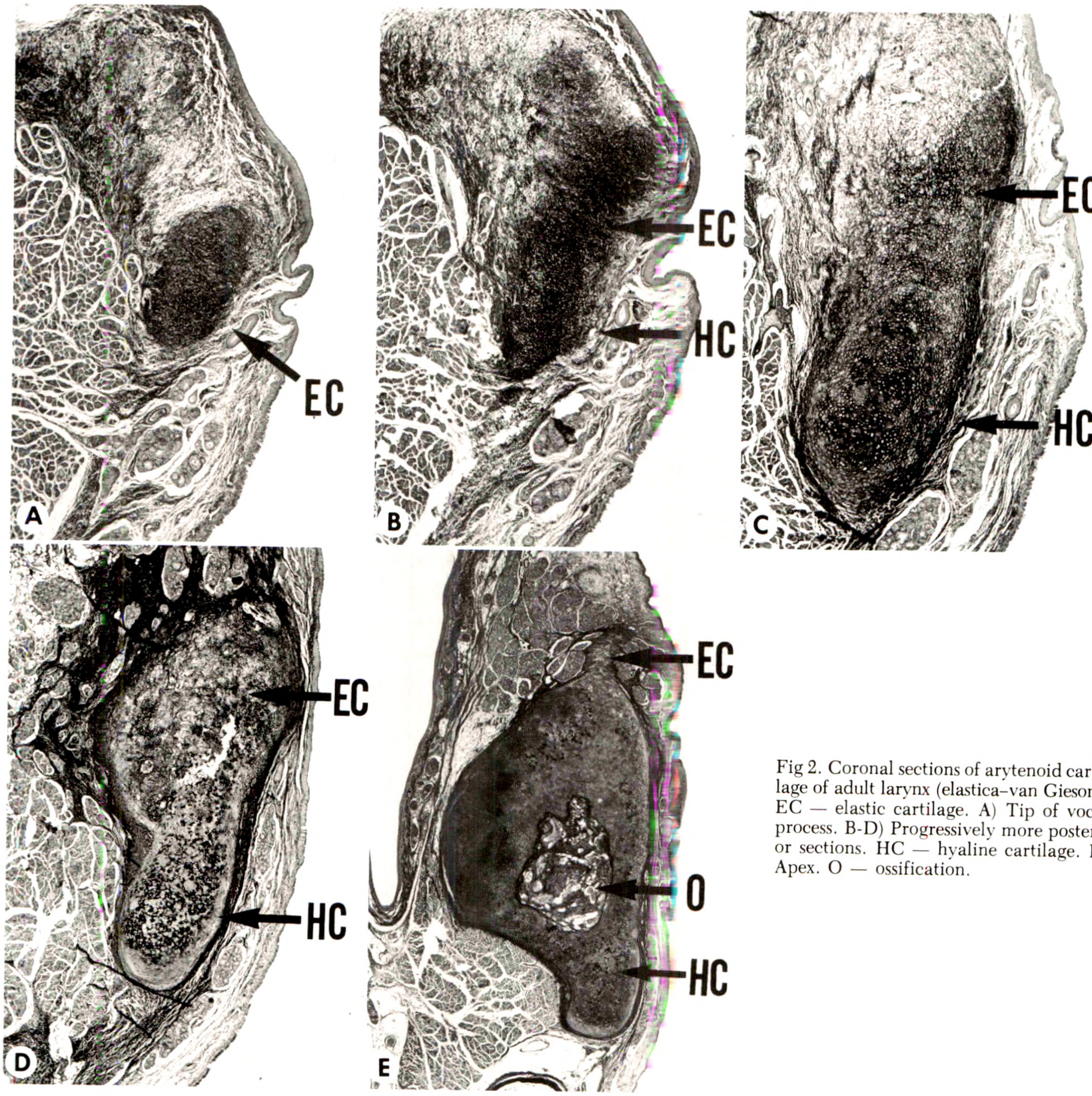

Fig 2. Coronal sections of arytenoid cartilage of adult larynx (elastica–van Gieson). EC — elastic cartilage. A) Tip of vocal process. B-D) Progressively more posterior sections. HC — hyaline cartilage. E) Apex. O — ossification.

higher magnification of the tip of the vocal process. The tip of the vocal process is composed of elastic cartilage. Figure 3C shows the transition area between the elastic and hyaline cartilage portions. Figure 3D shows a higher magnification of the hyaline cartilage portion.

Figure 4 shows coronal sections of the arytenoid cartilages of newborn larynges. The tip of the vocal process is composed only of elastic cartilage (Fig 4A). As the sections are followed posteriorly, the superior portion of the arytenoid cartilage is composed of elastic cartilage and the inferior portion of it is composed of hyaline cartilage (Fig 4B).

Similar to adult arytenoid cartilage, the tip of the vocal process and the superior portion of the arytenoid cartilage are composed of elastic cartilage. The transition between the elastic and hyaline cartilage portions is gradual, and the border between them is not clearly delineated.

In this way, elastic cartilage is found not only at the tip of the vocal process but at the superior portion of the arytenoid cartilage from the vocal process to the apex (Fig 5A). This phenomenon is observed at birth.

Behavior of Elastic Cartilage Portion of Arytenoid During Abduction and Adduction. Figure 5D shows a horizontal section of the vocal process during abduction. The vocal process bends concavely at the elastic cartilage portion during abduction.

Figure 5E shows a horizontal section of the vocal process during adduction. The vocal process bends convexly at the elastic cartilage portion during adduction.

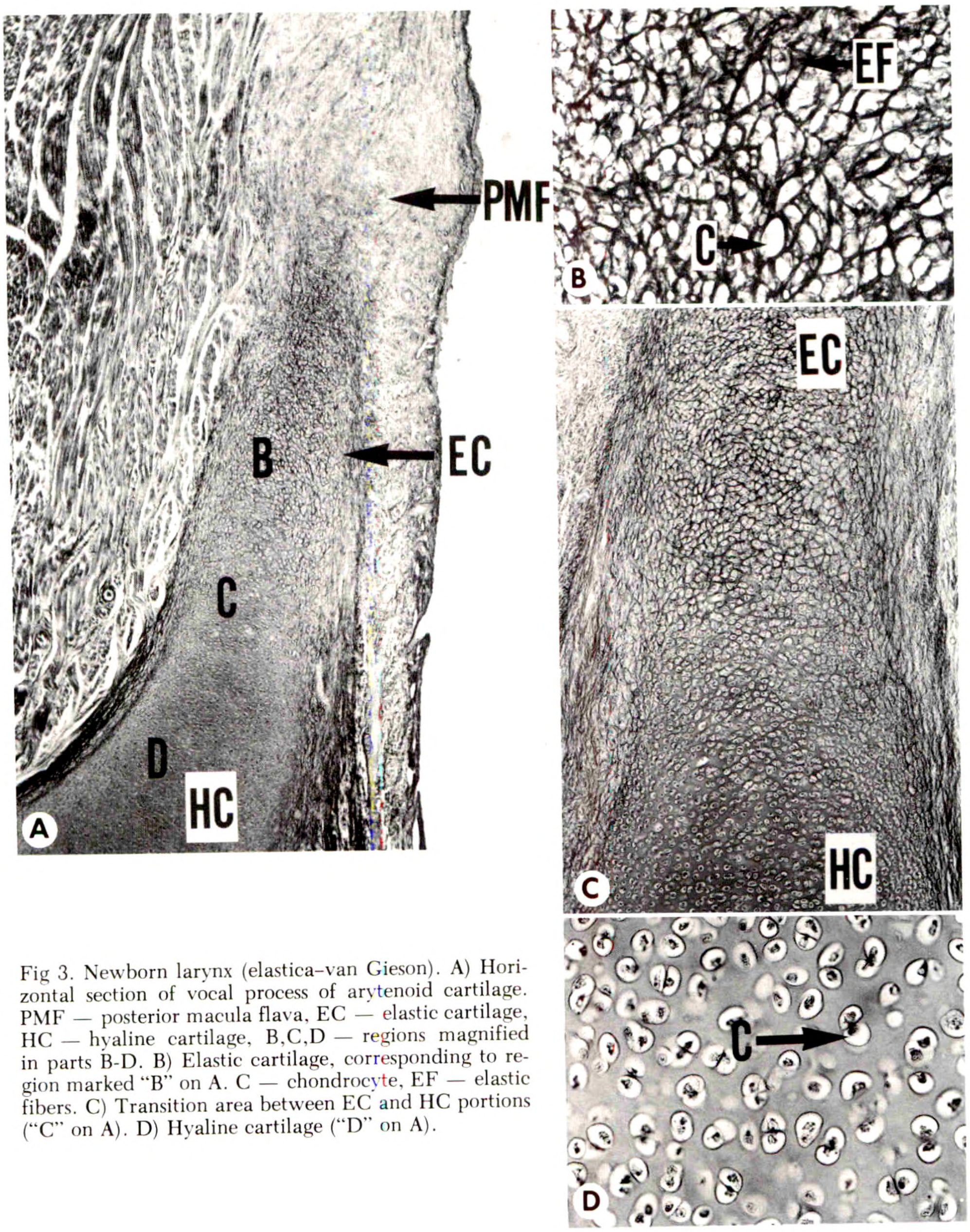

Fig 3. Newborn larynx (elastica–van Gieson). A) Horizontal section of vocal process of arytenoid cartilage. PMF — posterior macula flava, EC — elastic cartilage, HC — hyaline cartilage, B,C,D — regions magnified in parts B-D. B) Elastic cartilage, corresponding to region marked "B" on A. C — chondrocyte, EF — elastic fibers. C) Transition area between EC and HC portions ("C" on A). D) Hyaline cartilage ("D" on A).

Figure 5F shows a coronal section of the vocal process during adduction. The superior portion of the vocal process, ie, the elastic cartilage portion, protrudes more medially than the inferior portion of the vocal process, ie, the hyaline cartilage portion. The arytenoids come into contact mainly at their superior (ie, elastic cartilage) portions.

In this way, the vocal process bends at the elastic cartilage portion during adduction and abduction, and each side of the arytenoid comes into contact mainly at the elastic cartilage portion (Fig 5B,C).

DISCUSSION

The laryngeal cartilages consist chiefly of the thyroid, cricoid, arytenoid, and epiglottic cartilages. Of these cartilages, the thyroid and cricoid cartilages are composed of hyaline cartilage and the epiglottic cartilage is composed of elastic cartilage. Only the arytenoid cartilage is composed of both hyaline and elastic cartilage.

There is no general agreement on the distribution of elastic and hyaline cartilage in the arytenoid. Previous reports have described the tip of the arytenoids as being elastic cartilage,[1] the apex and vocal process as being elastic cartilage,[2,3] and the lower part of the arytenoids as being hyaline cartilage.[4]

Our investigation revealed that elastic cartilage was found not only at the tip of the vocal process, but also at the superior portion of the arytenoid cartilage, from the vocal process to the apex. The transition between elastic and hyaline cartilage portions is gradual, and the border between them is not

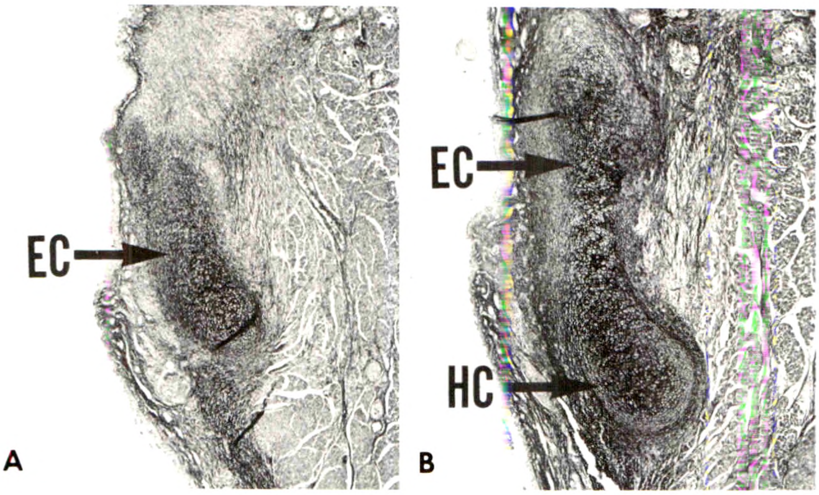

Fig 4. Coronal sections of vocal process of arytenoid cartilage of newborn larynx (elastica–van Gieson). EC — elastic cartilage. A) Tip of vocal process. B) Section posterior to A. HC — hyaline cartilage.

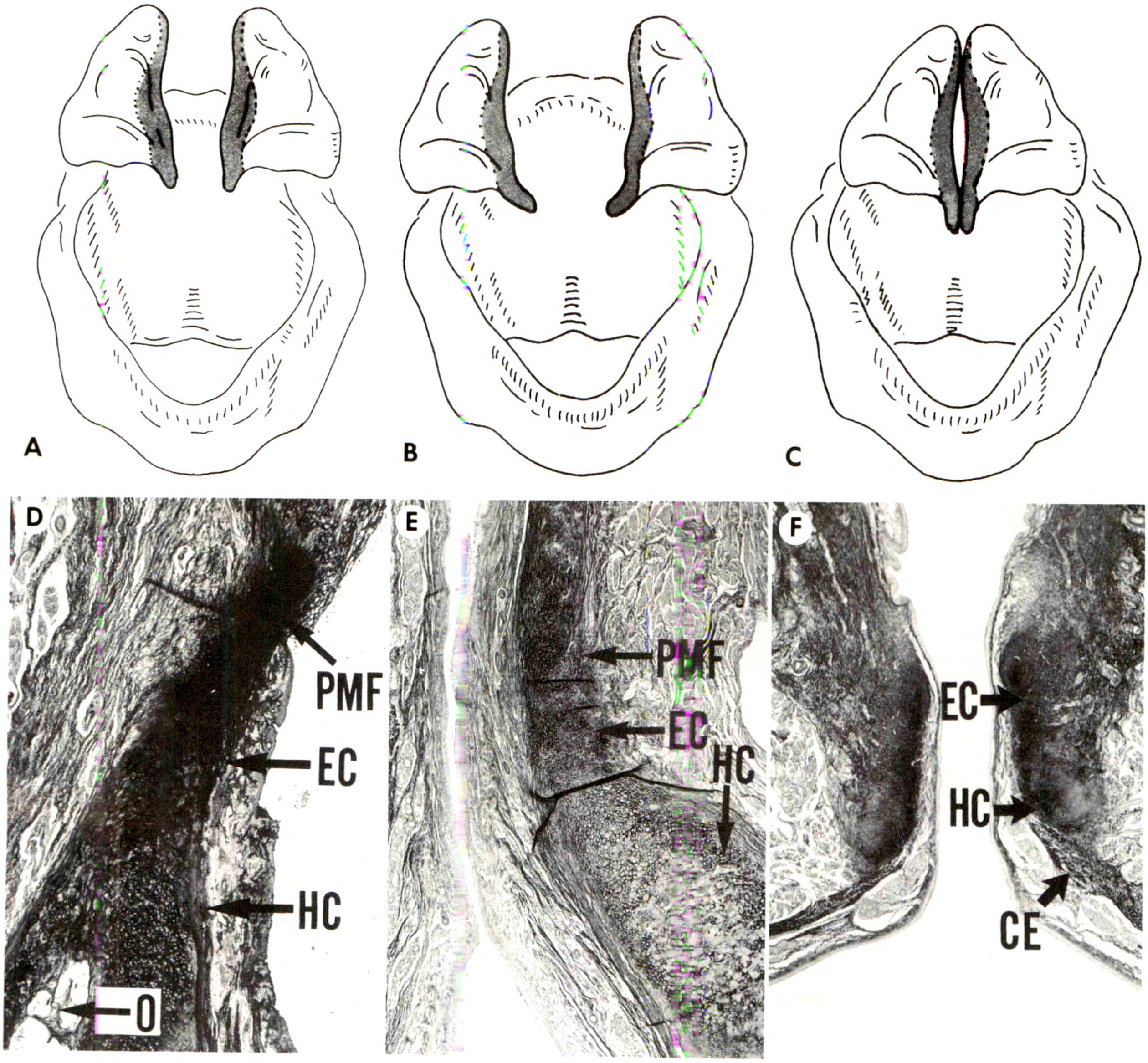

Fig 5. Distribution and behavior of elastic cartilage (EC) in arytenoids. A) Normal position (shaded) of EC. B) Elastic cartilage portion (shaded) during abduction. C) Elastic cartilage portion (shaded) during adduction. D) Horizontal section of vocal process during abduction (elastica–van Gieson). PMF — posterior macula flava, EC — elastic cartilage, HC — hyaline cartilage, O — ossification. E) Horizontal section of vocal process during adduction (elastica–van Gieson). F) Coronal section of vocal process during adduction (elastica–van Gieson). CE — conus elasticus.

clearly delineated. This phenomenon is observed at birth.

Elastic and hyaline cartilage have very different qualities, and so their relative distributions in the arytenoid cartilage are of interest in relation to their possible physiologic significance.

Hyaline cartilage, such as thyroid and cricoid cartilage, is firm and plays a role as a framework for the larynx. Similarly, the hyaline cartilage of the arytenoids is considered to function as a framework for the posterior glottis.[5]

Elastic cartilage, such as epiglottic cartilage, is soft and pliable. Our investigation reveals that the tip of the vocal process bends at the elastic cartilage portion during adduction and abduction, and that the arytenoids come into contact mainly at their superior portions, ie, the elastic cartilage portion. From the physiologic point of view, elastic cartilage located at the tip of the vocal process appears to facilitate movement of the vocal process during adduction and abduction, and elastic cartilage located at the superior portion of the arytenoids appears to act as a cushion whose purpose is to protect the arytenoids and covering mucosa from mechanical damage, which may be caused when the arytenoids come into contact.

Furthermore, the elastic cartilage portion never ossifies, hence elastic cartilage in the arytenoid is able to perform its role throughout an individual's lifetime.

In this way, elastic cartilage in the arytenoids appears to play an important role in the physiologic functioning of the arytenoids.

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PERILYMPH FISTULA:
A COMMON CAUSE OF DIZZINESS AND DYSEQUILIBRIUM?

A conference entitled Perilymph Fistula: A Common Cause of Dizziness and Dysequilibrium? will be held Sept 6-8, 1990, in Portland, Oregon. For further information, contact Sharon Newman, Conference Coordinator, Dept of Neuro-otology, Good Samaritan Hospital and Medical Center, 1040 NW Twenty-Second Ave, Portland, OR 97210; (503) 229-7348.

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TIME-RELATED CHANGES IN THE GUINEA PIG COCHLEA AFTER ACOUSTIC OVERSTIMULATION

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Forty-eight female pigmented guinea pigs were used to study the development of the morphologic and electrophysiologic changes occurring during a 4-week period after exposure to a 3.85-kHz pure tone at an intensity of 120 dB sound pressure level for 22.5 minutes. The morphologic results suggest an alteration in the permeability of ions between the inner ear fluids through gradual development of holes in the reticular lamina.

KEY WORDS — acoustic trauma, cochlear damage, compound action potential, morphology.

INTRODUCTION

During recent years many investigations have been performed in an effort to study the effects of acoustic trauma on the organ of Corti and to discern the mechanisms by which ultrastructural changes develop.[1-9] There have been reports showing continuing degeneration of the organ of Corti long after the cessation of various types of noise exposure such as impulse noise,[5] octave-band noise,[3] broadband noise,[1] and pure-tone exposures.[6,7] Most available information concerns the long-term effects of the acoustic trauma, whereas the early changes have not been equally well assessed.

Previous morphologic results have been correlated with the thresholds obtained in exposed and nonexposed animals.[6-8,10] The great variability between individual animals is a persistent problem for the investigator. The structural basis for the subject variance is still unclear. Cody and Robertson[11] observed an inverse relationship between the exposure and the variance among specimens. A constant relationship between permanent threshold shift N1 and hair cell damage was seen only in animals exposed to the highest sound intensity of 118 dB sound pressure level (SPL), and not after exposure to the lower sound intensities of 112 or 115 dB SPL.

The aim of the present study was to document the morphologic and electrophysiologic changes in the organ of Corti in order to evaluate the sequence of events that lead to the degeneration of the sensory organ.

MATERIAL AND METHODS

Forty-eight pigmented female guinea pigs were used. Eight animals were nonexposed controls, while 40 were exposed to a 3.85-kHz pure tone at 120 dB SPL for 22.5 minutes. The pure tone was generated by a low-distortion oscillator (SG 505 Tektronix, Beaverton, Ore) amplified by a Mosfet power amplifier and emitted from a high-efficiency horn loudspeaker in the ceiling of an anechoic chamber. The animals were able to move about freely within a wire mesh cage inside the chamber. The sound level within the cage was constant within ±1 dB, and each exposure was monitored with a calibrated microphone in the center of the cage. In eight of the animals, a permanent electrode was implanted in contact with the round window membrane of the right cochlea.[8,12] The thresholds of the compound action potential (CAP) N1 responses at 11 frequencies between 1 and 15 kHz were determined in all implanted animals. Four of the implanted animals were exposed to the 3.85-kHz pure tone, while the other four were nonexposed controls. The recovery of the CAP N1 thresholds was assessed by measuring pure-tone thresholds at 4 hours and 1, 2, 4, 7, 14, and 28 days after the exposure.

The 40 exposed animals were divided into five groups of eight animals each. One group was killed painlessly at each of the following postexposure times: immediately, 4 hours, 1 day, 5 days, and 28 days. These postexposure times were chosen in order to observe the early morphologic changes that take place on the surface of the organ of Corti and to follow the development of these changes until no further signs of degeneration could be observed.

After the animal was killed, both cochleas were removed promptly and fixed in 3% glutaraldehyde in sodium-phosphate buffer. The right cochlea was used for light microscopic analysis and transmission electron microscopic studies of the damaged areas in the organ of Corti. The left cochlea was processed according to the tannin-fixation method[13] and dissected for scanning electron microscopy (SEM) according to standard methods. The hair cell damage was graded over 0.1-mm segments of the organ

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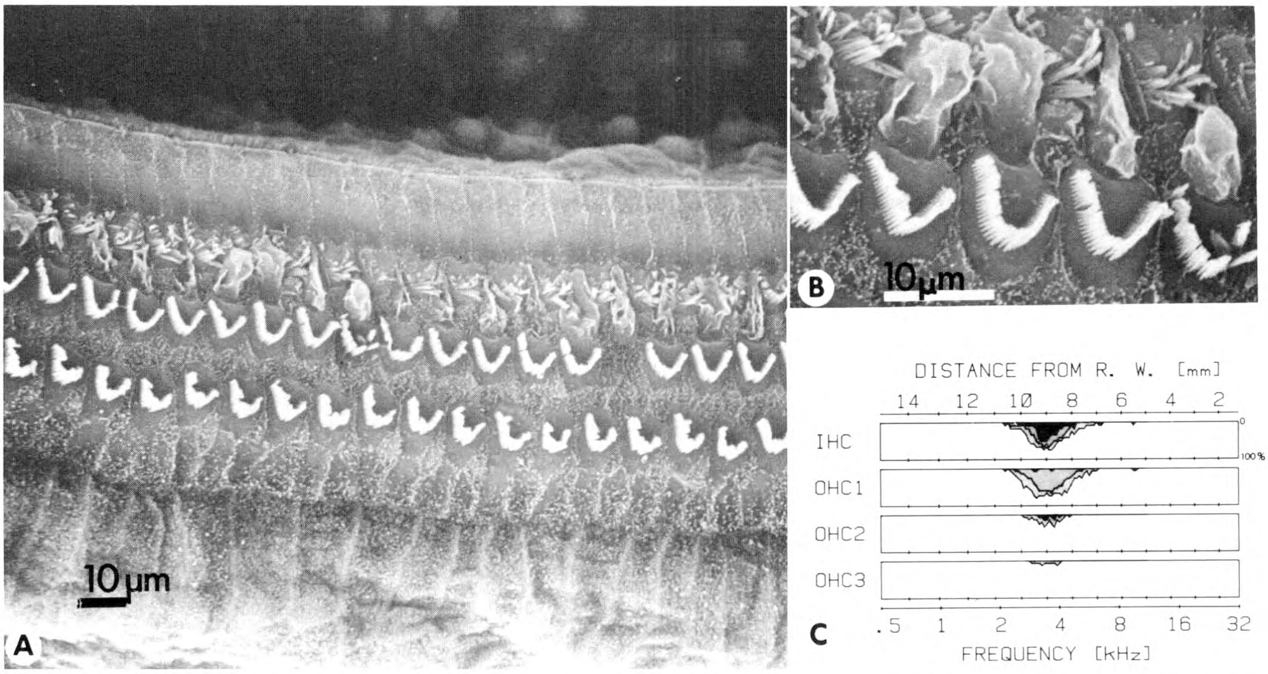

Fig 1. Effects of acoustic trauma immediately after cessation of acoustic overstimulation. Grade 1 to 3 damage was evident. A) Scanning electron micrograph of outer hair cells (OHCs). Disarray of stereocilia and protrusions are evident in first row of OHCs, while second row is relatively undisturbed. B) Higher-magnification micrograph showing morphologic changes in first and second OHC rows. C) Values of mean number of damaged hair cells in different grades (n = 8 [animals]). Each grade of damage is recorded for each 0.1-mm segment of the organ of Corti for all eight animals. Grade 1, 10% to 50% damage to or loss of individual stereocilia (light gray). Grade 2, 50% to 100% damage to or loss of individual stereocilia (medium gray). Grade 3, loss of individual hair cells (dark gray). R.W. — round window.

of Corti in an area 3 to 14 mm distant from the round window membrane (RW). This distance corresponds to 16% to 76% of the distance along the organ of Corti measured from the level of the RW. The structural changes were judged according to a four-point scale by use of the following criteria: grade 1, 10% to 50% damage to or loss of individual stereocilia; grade 2, 50% to 100% damage to or loss of individual stereocilia; grade 3, no cuticular plate visible, or missing hair cell; and grade 4, total loss of the organ of Corti. The mean number of the different grades of hair cell damage was recorded

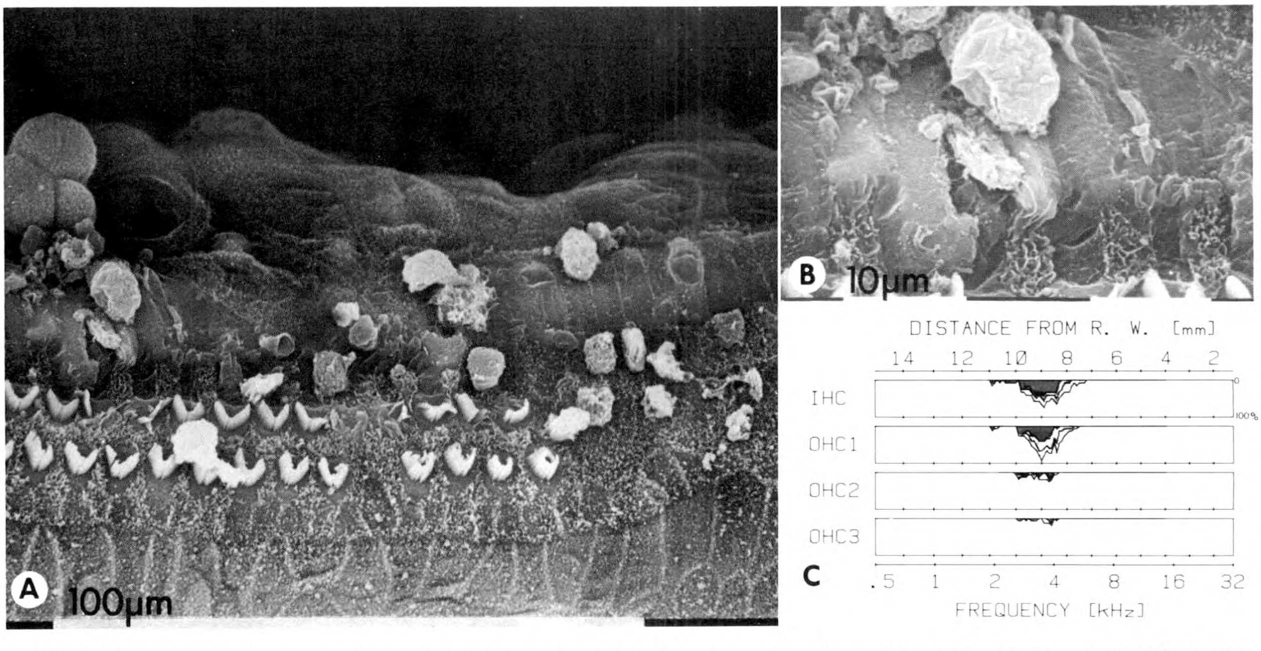

Fig 2. Effects of acoustic trauma 4 hours after exposure. Grade 1 to 3 damage was evident. A) Scanning electron micrograph of area of maximum damage in organ of Corti. Stereociliary disturbances and missing hair cells are present in all rows, as well as multiple protrusions in reticular lamina. B) Higher-magnification micrograph showing damaged reticular lamina. C) Values of mean number of damaged hair cells in different grades (n = 8 [animals]). Symbols as in Fig 1C.

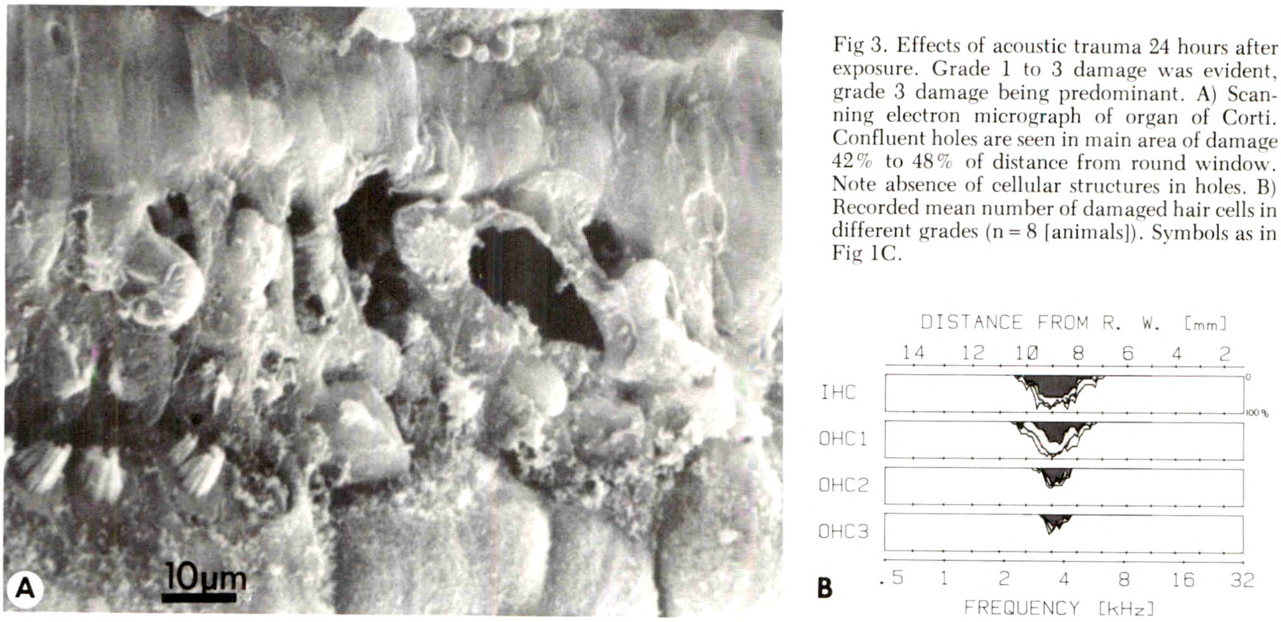

Fig 3. Effects of acoustic trauma 24 hours after exposure. Grade 1 to 3 damage was evident, grade 3 damage being predominant. A) Scanning electron micrograph of organ of Corti. Confluent holes are seen in main area of damage 42% to 48% of distance from round window. Note absence of cellular structures in holes. B) Recorded mean number of damaged hair cells in different grades (n = 8 [animals]). Symbols as in Fig 1C.

from the eight animals in each group and plotted for each segment. The inner hair cells (IHCs) and outer hair cells (OHCs) were analyzed separately in each group of animals. The morphologic data were analyzed statistically. The difference in the amount of damage between the groups of animals was tested with multiple, stepwise regression analysis to investigate whether or not any significant differences could be found that were related to survival time.

RESULTS

Scanning Electron Microscopy. As a general pattern in the control group, only sporadic loss of OHCs was observed. On average, 10 to 15 OHCs were missing in the 3- to 14-mm area of the organ of Corti. No grade 1, 2, or 4 damage was observed in this material. A common finding was a floppiness and irregularity of the stereociliary bundles in the OHCs of the two apical turns. This phenomenon was noted predominantly in the third row of OHCs. In the group of animals killed immediately (ie, approximately 5 minutes) after exposure, the damage was limited mainly to IHCs and the first row of OHCs in the area 38% to 56% of the distance from the RW. Damage to or loss of stereociliary structures as well as blebs bulging from the cuticular plate was noted (Fig 1).

At 4 hours after exposure, the grade 3 damage had spread to involve all OHC rows. Degeneration of the surrounding supporting cells also was seen. In this group, holes appeared in the reticular lamina. Grade 3 damage was found more often at 4 hours

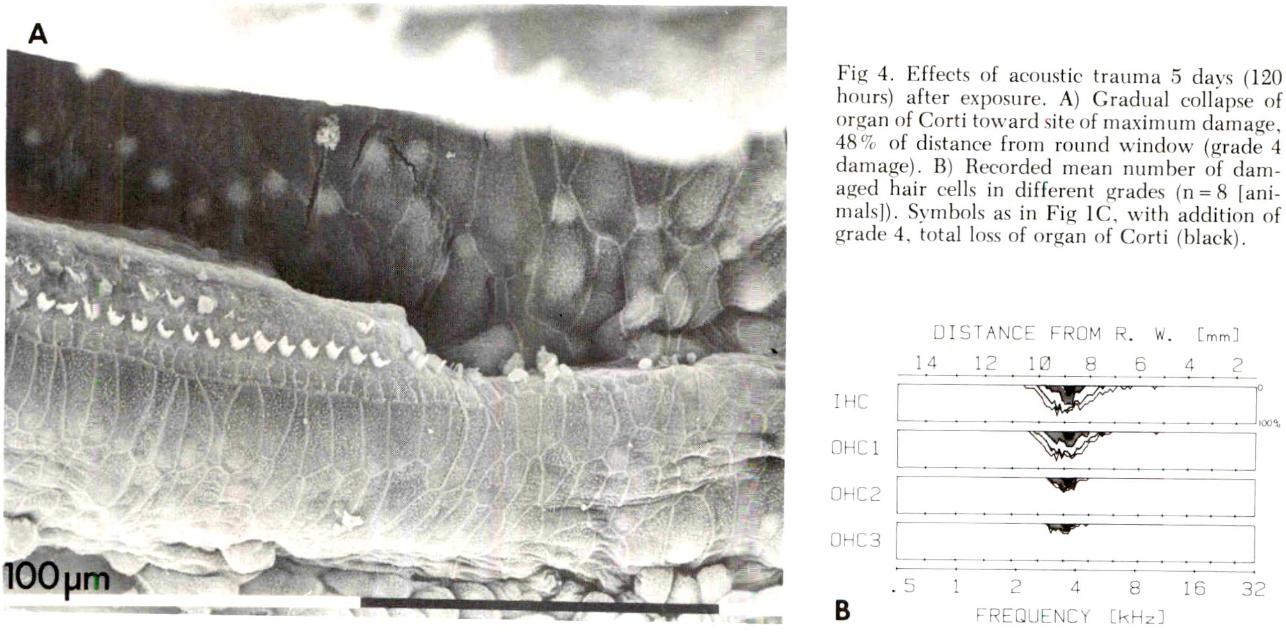

Fig 4. Effects of acoustic trauma 5 days (120 hours) after exposure. A) Gradual collapse of organ of Corti toward site of maximum damage, 48% of distance from round window (grade 4 damage). B) Recorded mean number of damaged hair cells in different grades (n = 8 [animals]). Symbols as in Fig 1C, with addition of grade 4, total loss of organ of Corti (black).

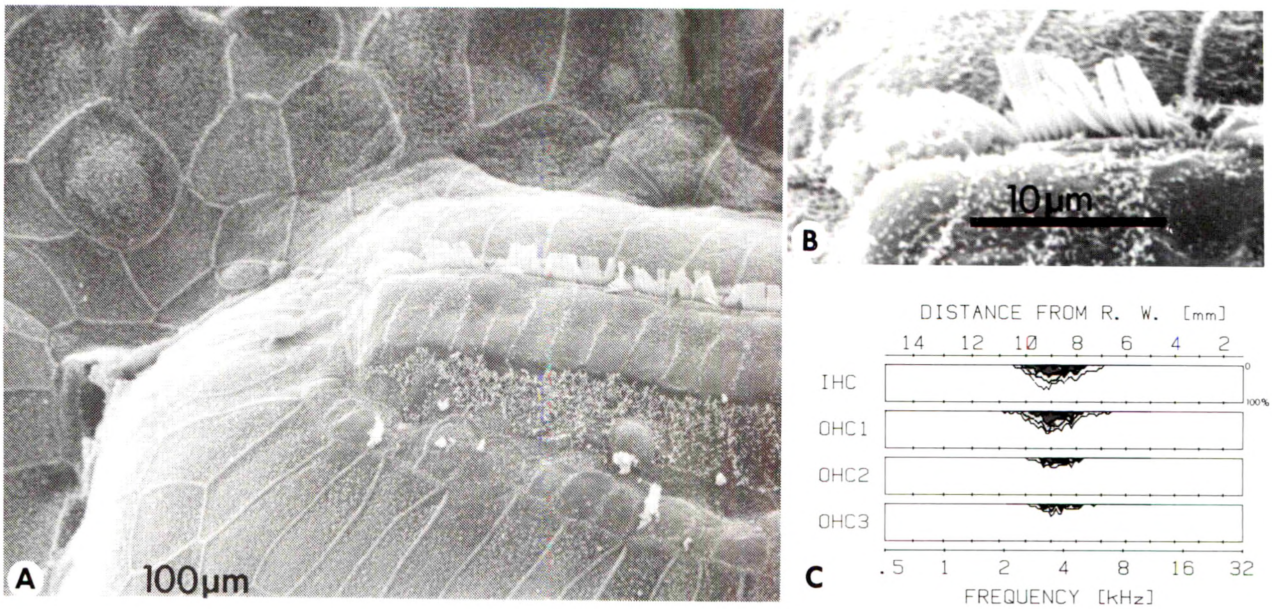

Fig 5. Effects of acoustic trauma 28 days (672 hours) after exposure. A) Total disruption of organ of Corti (42% of distance from round window). Gradual normalization of epithelium basal to grade 4 damage is obvious. B) Higher magnification of area basal to grade 4 damage, where sterocilia bundles of inner hair cells reappear. C) Increasing amount of grade 4 damage is evident as compared with other groups (n = 8 [animals]). Symbols as in Figs 1C and 4C.

than in the specimens studied immediately after the exposure (Fig 2).

In the 24-hour group, the damaged area involved a large segment 42% to 48% of the distance from the RW. An increasing number of cells with grade 3 damage were evident. Compared with the 4-hour group, marked degeneration of both sensory and supporting cells had now taken place (Fig 3).

In the 5-day (120-hour) postexposure group, grade 4 damage had developed in the area of maximal damage (Fig 4). This region demonstrated the most severe changes in the organ of Corti. In areas located apical and basal to this region, protrusions from the cuticular plate of the OHCs were found.

In the 28-day (672-hour) group, no further signs of continuing degeneration could be identified on the surface of the organ of Corti as compared with the 5-day group. Figure 5 shows the maximally damaged area located 40% to 50% of the distance from the RW, with an unchanged damage pattern both apical and basal to this area, even though the extension of grade 4 damage had increased.

Light and Transmission Electron Microscopy. Five minutes after exposure, ciliary disarrangement

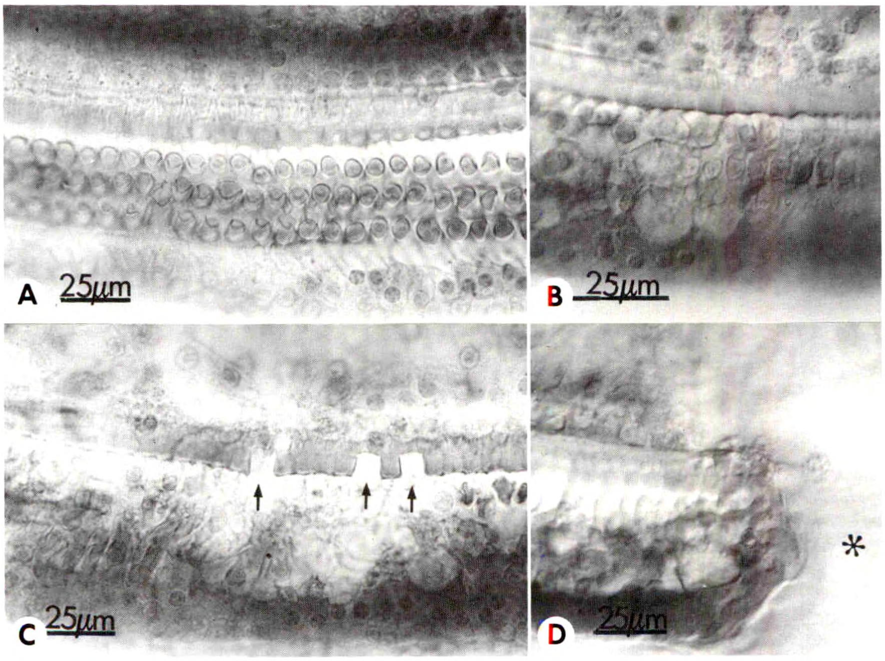

Fig 6. Phase-contrast photomicrographs of area 42% to 48% of distance from round window. A) Immediately (5 minutes) after exposure, stereociliary disarray and deformation of both inner and outer hair cells can be observed. B) Four hours after exposure, irregularity in hair cell rows and swollen outer hair cells with deformed nuclei have appeared. C) Twenty-four hours after exposure, area with translucent hair cells has developed, and frequent loss of pillar cells is evident (arrows). D) Five days after exposure, total loss of organ of Corti is evident in area of maximal damage. Flat epithelium (*) has replaced normal epithelium, with gradual collapse of epithelium toward this area.

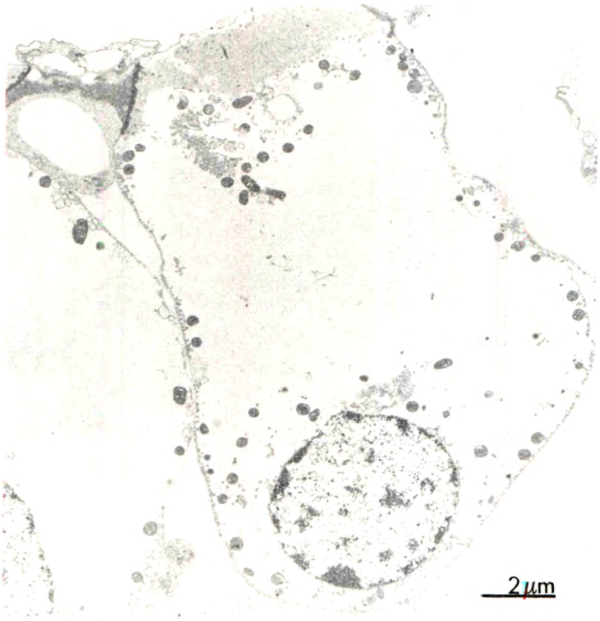

Fig 7. Transmission electron micrograph from area of maximal damage 4 hours after exposure to 3.85-kHz pure tone. Swollen outer hair cell with degenerative changes in nucleus and cytoplasm is visible. Irregularity in cuticular plate is evident. Reticular lamina is irregular.

was evident in both IHCs and OHCs (Fig 6A). Intracellular changes were rare, however, though early changes with deformation of both IHCs and OHCs were demonstrated, while the infranuclear and synaptic regions of the hair cells appeared unaffected. The inner and outer phalangeal cells displayed edema and swelling, while the pillar cells showed no signs of degenerative changes.

Four hours after exposure, a marked intracellular edema had developed in both IHCs and OHCs (Figs 6B and 7). Cuticular protrusions and ruptures were seen in both cell types. As in the 5-minute group, edema and swelling was also evident in the surrounding supporting cells. Loss of pillar cells was seen as well.

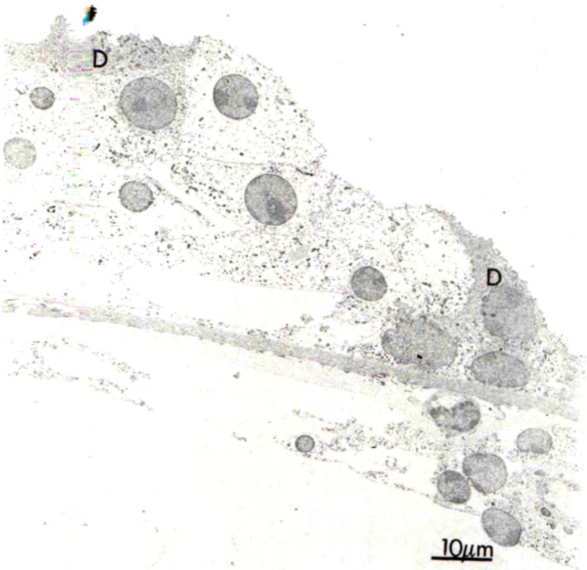

Fig 8. Transmission electron micrograph of section of organ of Corti close to area of maximal damage, where normal epithelium is replaced by flat epithelium. Hair cells have degenerated, leaving supporting cells to cover loss of hair cells in reticular lamina. Darkly stained cells (D) are demonstrated, filling part of surface.

After 24 hours, a further progression of the degenerative changes could be seen (Fig 6C). Ruptures in both plasma membranes and cuticular plates of IHCs and OHCs were frequently observed. The edema and swelling had progressed, together with the occurrence of an increased granulation in the cytoplasm of the surrounding supporting cells. Loss of pillar cells was frequently seen, as well as displacement of pillar heads, leaving an open passage between the endolymphatic and perilymphatic spaces.

After 5 days (120 hours) an area of total degeneration had occurred in the middle of the area of maximal damage (Fig 6D). In the border zone of

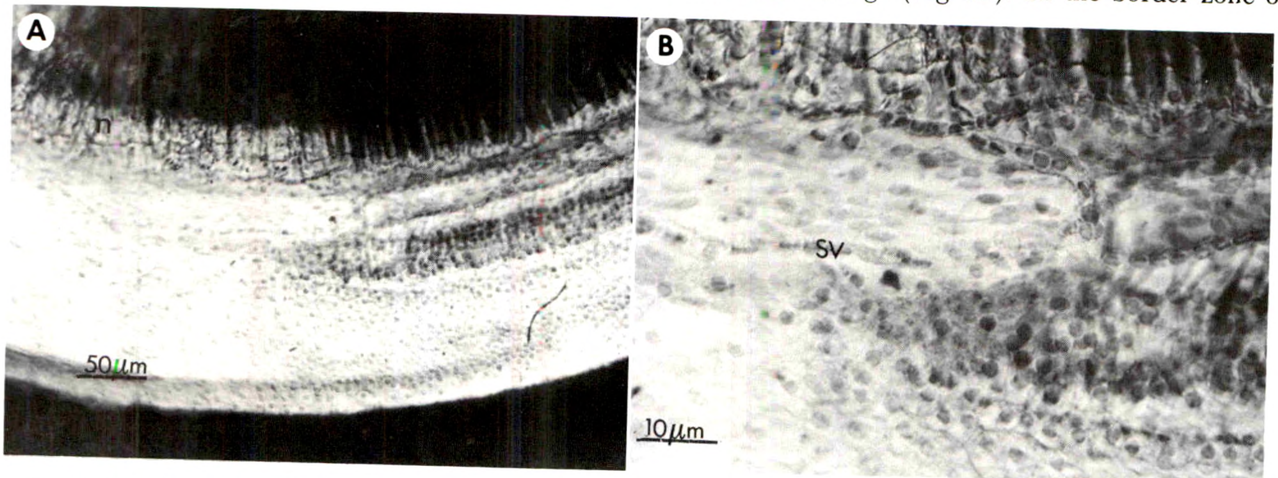

Fig 9. A) Light micrograph of area of maximal damage 4 weeks after sound exposure. Flat epithelium has replaced normal epithelium. Loss of nerve fibers (n) is evident. B) Higher-magnification micrograph of border zone between normal epithelium and flat epithelium, illustrating degeneration of organ of Corti. Spiral vessel (SV) below basilar membrane is clearly visible.

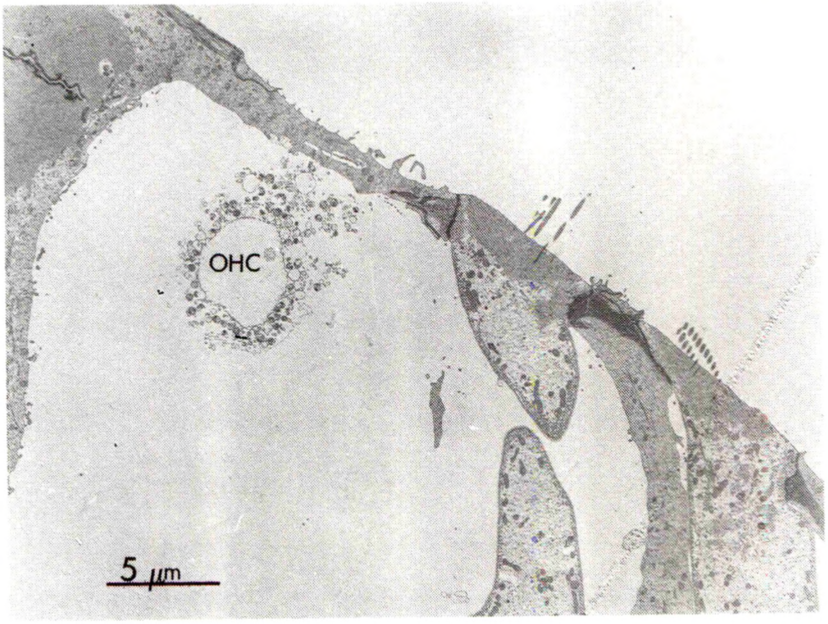

Fig 10. Transmission electron micrograph displaying reconstructed reticular lamina in outer hair cell region, covering degenerating remnant of one outer hair cell (OHC) in first row.

the flat epithelium that had replaced the normal organ of Corti, all stages of degeneration described during the first day after exposure were found. Both apical and basal to this area, signs of degeneration, but also repair, were evident in that Hensen's cells, Deiters' cells, border cells, and darkly stained cells replaced areas formerly occupied by the sensory epithelium (Fig 8). Darkly stained cells that were filled with densely packed granules were found at the level of both IHCs and OHCs. The number of intracellular dense bodies was also increased in both the inner and the outer phalangeal cells.

Four weeks after the exposure, an area of total degeneration of the organ of Corti replaced with a flat epithelium was generally observed in the entire area of maximal damage (Fig 9). Degenerative changes in the form of swollen and distorted hair cells with stereociliary changes were evident in the sensory epithelium apical and basal to this area. Remnants of degenerating OHCs could be observed below the newly formed reticular lamina (Fig 10). As observed in the 5-day group, the reticular lamina had been rearranged by an ingrowth of the surrounding supporting cells. The pillar cells in the

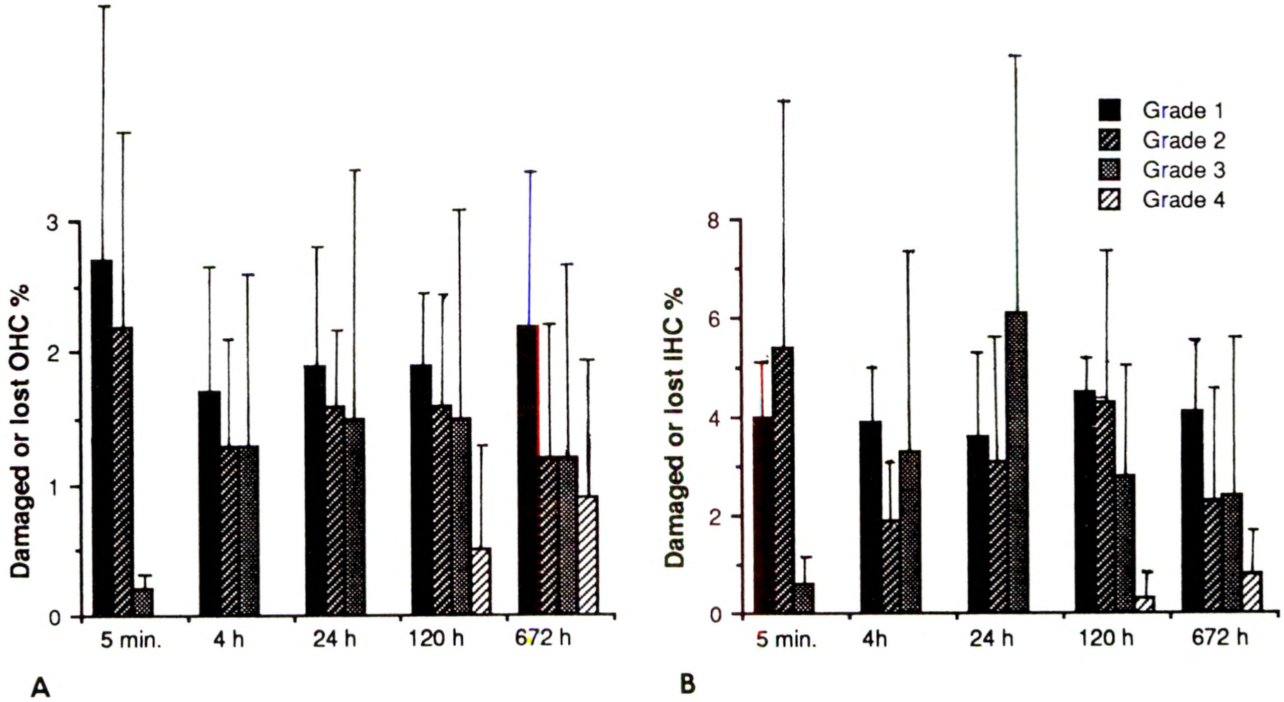

Fig 11. Percentage of damaged hair cells in organ of Corti at different postexposure times. A) Outer hair cells. B) Inner hair cells.

TABLE 1. PERCENT DAMAGED AND MISSING HAIR CELLS (MEAN ± SD)

	5 Minutes	*4 Hours*	*24 Hours*	*5 Days*	*28 Days*
Inner hair cells					
Grade 1	4.0 ± 1.1	3.9 ± 1.1	3.6 ± 1.7	4.5 ± 0.6	4.1 ± 1.4
Grade 2	5.4 ± 5.1	1.9 ± 1.2	3.1 ± 2.5	4.3 ± 3.0	2.3 ± 2.2
Grade 3	0.6 ± 0.5	3.3 ± 4.1	6.1 ± 5.2	2.8 ± 2.2	2.4 ± 3.1
Grade 4	0	0	0	0.3 ± 0.6	0.8 ± 0.9
Outer hair cells					
Grade 1	2.7 ± 1.8	1.7 ± 0.9	1.9 ± 0.8	1.9 ± 0.6	2.2 ± 1.2
Grade 2	2.2 ± 1.4	1.3 ± 0.8	1.6 ± 0.6	1.6 ± 0.8	1.2 ± 1.0
Grade 3	0.2 ± 0.1	1.3 ± 1.3	1.5 ± 1.9	1.5 ± 1.6	1.2 ± 1.4
Grade 4	0	0	0	0.5 ± 0.8	0.9 ± 1.0
Grade 3 damage					
Inner hair cells	0.6 ± 0.5	3.3 ± 4.1	6.1 ± 5.2	2.8 ± 2.2	2.4 ± 3.1
Outer hair cells 1	0.4 ± 0.4	2.7 ± 3.0	4.0 ± 3.0	2.4 ± 2.6	2.1 ± 2.4
Outer hair cells 2	0.1 ± 0.1	0.8 ± 1.0	2.1 ± 1.7	1.2 ± 1.7	0.8 ± 1.2
Outer hair cells 3	0.1 ± 0.1	0.5 ± 0.5	1.5 ± 1.2	0.8 ± 1.2	0.7 ± 1.0

For damage grades, see text.

damage areas showed various degrees of fibrillar degeneration and displacement causing a general flattening of the organ of Corti.

Statistical Evaluation of Scanning Electron Microscopy Findings. The mean values and standard deviations of the percentages of damaged sensory cells were obtained after quantitative assessment of each grade of damage. The mean percentage of damaged cells for each grade counted in 0.1-mm segments along the organ of Corti at each separate postexposure interval is presented in Fig 11 and Table 1. The percentage of damaged hair cells along the organ of Corti was estimated from the normative values for the total numbers of OHCs and IHCs, ie, 7,500 and 2,050, respectively.[14-16] The number of missing hair cells in grade 4 damage areas was estimated from the average number of hair cells normally present in the missing part of the organ of Corti. When we compared postexposure time intervals (5 minutes, 4 hours, and 24 hours), a gradual increase in grade 3 damage was evident. This development was statistically significant ($p < .05$) for both IHCs and OHCs. In the 5-day (120-hour) group, an increase in grade 4 damage and a corresponding decrease in grade 3 damage was evident. The amount of grade 4 damage showed further increases in the 28-day (672-hour) group, with a concomitant decrease in the grade 3 damage. This development could be found in both IHCs and OHCs. There was no significant difference between grade 3 damage in the 24-hour group compared with the sum of grade 3 and 4 damage in the 5- and 28-day groups. The amount of grade 1 and 2 damage remained relatively constant throughout the recovery period.

A constant observation of the damage pattern of the individual animals was the occurrence of one or two animals in each group exhibiting very slight damage. The rest of the specimens within each group showed a uniform damage pattern. The standard deviations were large in this material, as illustrated in Fig 11. To further investigate the grade 3 damage over time, individual registrations of hair cells for each hair cell row were submitted to regression analysis (Fig 12). The values were transformed to natural logarithm values before analysis. The development of damage was evident in all hair cell rows. A significant difference ($p < .05$) in the amount of grade 3 damage was found in all hair cell rows between the 5-minute and 24-hour groups.

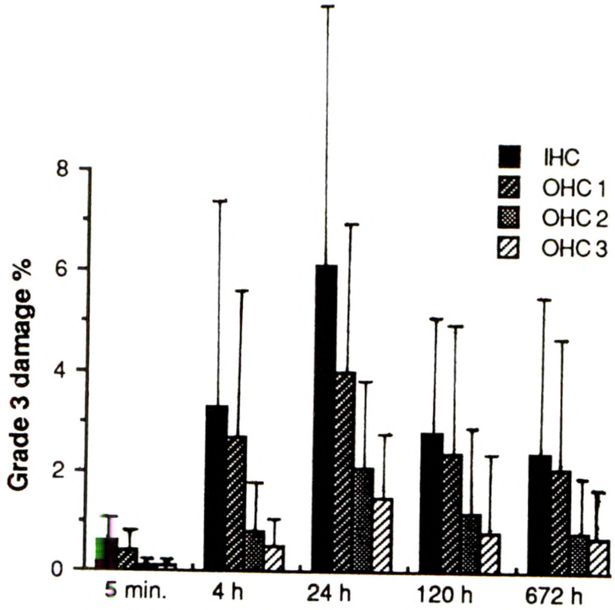

Fig 12. Percentage of grade 3 damage in inner hair cells and three rows of outer hair cells in organ of Corti at different postexposure times.

Electrophysiology. During the first 7 days after exposure, the CAP N1 thresholds showed considerable recovery from the values obtained 4 hours after exposure. As indicated in Fig 13, a threshold shift

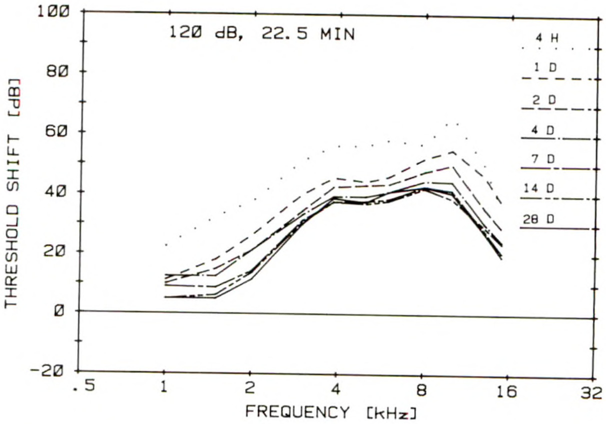

Fig 13. Mean compound action potential N1 thresholds recorded at 11 frequencies from 1 to 15 kHz at intervals of measurement from 4 hours to 28 days (672 hours) postexposure.

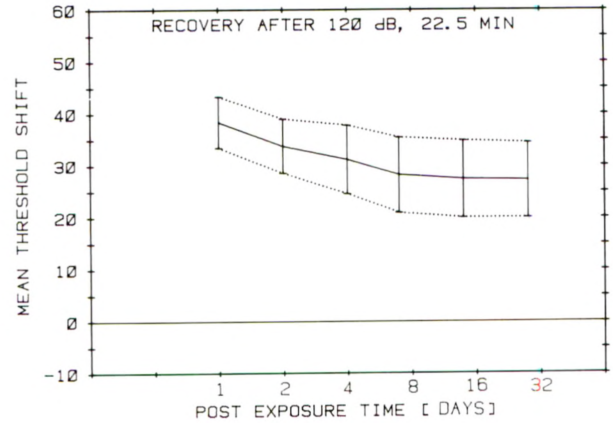

Fig 14. Mean threshold shift ± SD for 11 frequencies from 1 to 15 kHz, 1 to 28 days after exposure.

(TS) of 60 dB was recorded 4 hours after the 3.85-kHz exposure for the frequencies between 4 and 10 kHz. At lower and higher frequencies, the TS was smaller: 20 dB at 1 kHz and 40 dB at 15 kHz. With an increase of the postexposure time, a decrease in the TS resulted until it stabilized at a level of 40 dB between 4 and 10 kHz, 5 dB at 1 kHz, and 20 dB at 15 kHz, 7 days postexposure. The mean TSs for the 11 frequencies from 1 to 15 kHz were estimated at the different time intervals after exposure, taking into account the corresponding standard deviation (Fig 14 and Table 2). A correlation matrix with tests of significance was used to correlate the morphologic and electrophysiologic results. The best correlation between TS and the morphologic damage was found in the 3- and 3.85-kHz region, ie, the area of maximum structural change in the organ of Corti.

TABLE 2. MEAN COMPOUND ACTION POTENTIAL N1 THRESHOLD SHIFT

Day	*Threshold Shift (dB Sound Pressure Level)*
1	38 ± 4.5
2	34 ± 5.0
4	31 ± 6.0
7	29 ± 7.0
14	28 ± 7.5
28	28 ± 7.0

DISCUSSION

In the present study the time sequence of the degeneration of the organ of Corti was analyzed by use of a four-point system[8,9] to evaluate the ultrastructural changes as revealed by SEM. At the sound exposure level (120 dB SPL for 22.5 minutes) used in this study, all four grades of damage were found. This method of grading the damage allows a detailed analysis of the surface morphology of the organ of Corti.

In the present investigation, holes in the reticular lamina could not be found immediately after exposure. Grade 1 and 2 damage and bulging of the cuticular plate into the scala media were found at this early stage. Ruptures of the cuticular plate and development of holes in the reticular lamina were visible 4 hours after exposure. The extension of damage along the organ of Corti seemed unchanged after the first postexposure day. Grade 1 and 2 damage showed little variation, while the findings suggest transformation of grade 3 damage into grade 4 damage during the period following.

Earlier investigators have described the development of ultrastructural changes in the organ of Corti after acoustic overstimulation. Thorne and Gavin[6] suggested that some hair cells devoid of stereocilia that were damaged immediately after exposure did not degenerate until 28 days postexposure. Hamernik et al[5] described ongoing degenerative changes 30 days after exposure to high-intensity impulse noise. These observations indicate a progressive degeneration that extends over a much longer period of time.

Bohne and Rabbitt[17] described short-term effects (1 to 2 hours) on the organ of Corti of the chinchilla after exposure to an octave-band noise at 108 dB SPL for 3.5 hours. Holes in the reticular lamina were observed suggesting a mixing of endolymph and perilymph that could create a toxic environment for the hair cells. In contradiction to this, Hunter-Duvar[18] did not observe the development of holes in the reticular lamina after 120-dB pure-tone exposure in the chinchilla, either immediately or at time intervals ranging to 10 weeks after exposure.

It has been proposed by Konishi et al[19] that ionic permeability changes of the endolymph-perilymph barrier are a significant factor in the physiologic mechanisms underlying noise-induced hearing loss. The development of the structural changes demonstrated in the present study, in the form of multiple holes in the reticular lamina, also supports the idea that such a fluid mixing mechanism may take place in the organ of Corti after acoustic overstimulation. However, changes in the form of stereociliary disarray and protrusions in the reticular lamina immediately after exposure indicate that other mechanisms initiate the development of degeneration following acoustic trauma. At this early stage, no signs of artificial communication between the fluid compartments in the organ of Corti were evident. Therefore, metabolic changes, including a disturbed transport of ions into and out of the hair cells, may be responsible for the early morphologic and resulting functional changes in the hearing organ.

The frequency-place map used in this study was derived from the results of earlier investigations.[20-22] The morphologic changes, according to these measurements, were located in the expected region of the cochlea, though the greatest N1 threshold shift occurred at frequencies higher than the exposure frequency. The phenomenon of a high-frequency shift has been demonstrated earlier by several investigators.[6,7] The most common explanation for this discrepancy is the possibility of more subtle metabolic or micromechanical abnormalities in the hair cells corresponding to these higher frequencies.

The relationship between cochlear morphology and electrophysiologic measurements has been discussed earlier in conjunction with various exposure parameters. Robertson[23] reported normal N1 thresholds in spite of damaged OHC stereocilia. Stereociliary disarray has been found to be the best morphologic correlate to the loss of auditory sensitivity.[4,10,23] In the present study a decrease in TS occurred during the first 7 days after exposure. During the same period of time, a grade 4 injury appeared, as seen in the morphologic study. The relatively slight damage seen immediately after exposure cannot be solely responsible for the large N1 TS demonstrated in Figs 13 and 14.

The best correlation between hair cell damage and CAP N1 TS could be demonstrated in the region corresponding to the exposure frequency. At higher frequencies, no such correlation could be found. As indicated in Fig 13, the greatest decrease in TS occurred during the first day after exposure. After this the maximum extension of the damaged area could be seen along the organ of Corti, as observed by SEM.

During the development of structural changes in the organ of Corti, large individual differences often have been reported. This was also the case in the present study. The results, however, support the suggestion[17] of a leakage of ions into the fluid spaces of the organ of Corti through ruptures in the reticular lamina developed after acoustic trauma, which may add to the progressing pathologic changes in the sensory and supporting cells. The cause of degeneration seems to be a gradual spread of damage to the sensory cells and ultimately to the supporting cells and nerve fibers. This degeneration takes a comparatively long time to develop. Further studies are needed, particularly on the ultrastructural level, in order to explain the possible intracellular changes causing both temporary functional changes and the progressive degeneration of the sensory epithelium in the organ of Corti following acoustic trauma.

SUMMARY

This study suggests that the early changes in the hair cells progress to total hair cell loss in some instances, while other cells survive in a partly damaged condition. This morphologic process seems to occur during the first week after noise exposure. A complete degeneration of the organ of Corti, ie, grade 4 damage, could be demonstrated 5 days after exposure, while the maximum amount of hair cell loss had already developed after 24 hours. During the first week, the TS decreases and stabilizes, with a resultant permanent TS. The best correlation between TS and morphologic damage could be found at the region of the exposure frequency. In the high-frequency region, no such correlation could be found.

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Ann Otol Rhinol Laryngol 99:1990

ENDOTOXIN AND LYSOSOMAL PROTEASE ACTIVITY IN ACUTE AND CHRONIC OTITIS MEDIA WITH EFFUSION

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Endotoxin levels and lysosomal protease (collagenase, cathepsin B, and lysozyme) activity were measured in 104 middle ear effusions (MEEs) from patients with otitis media with effusion (OME). The MEE samples were classified into four groups: pediatric serous, mucoid, and acute, and adult serous. Endotoxin levels and lysosomal protease activity in MEEs were significantly different in the following order: adult < serous < mucoid < acute groups, indicating that both endotoxin and lysosomal proteases are more closely related to the pathogenesis of pediatric chronic OME than to adult OME. In pediatric serous and mucoid effusions, endotoxin level had a significant correlation with activity of the lysosomal proteases. In conclusion, endotoxin enhances leukocyte infiltration into the middle ear, and lysosomal proteases released from leukocytes damage the middle ear mucosa and thereby prolong mucosal inflammation, which may be responsible for delayed recovery from acute OME.

KEY WORDS — endotoxin, lysosomal proteases, otitis media with effusion.

INTRODUCTION

Otitis media with effusion (OME) is one of the most prevalent middle ear diseases, characterized by effusions in the middle ear cavity.[1] Both eustachian tube dysfunction and repeated bacterial infections are known to be major etiologic factors in OME.[2-4] Various biochemical, immunologic, and bacteriologic parameters have been analyzed to identify the significant factors contributing to the chronicity of OME.

Endotoxin, a lipopolysaccharide derived from cell walls of gram-negative bacteria, for example *Hemophilus influenzae*, is found in middle ear effusion (MEE). Several investigators have reported that the endotoxin level in MEE is one of the parameters reflecting the chronicity of OME in children.[5-8]

Lysosomal proteases in the middle ear mucosa and MEE have been shown to play significant roles during the disease processes of OME, because their proteolytic activity causes tissue damage and prolongs middle ear inflammation by activating proenzymes (kininogen and plasminogen) and the complement system.[9-11] Lysosomal proteases seem to suppress the recovery from acute OME unless they are inactivated by protease inhibitors.[12,13] Study of the relationships between significant parameters relating to the chronicity of OME may provide a way to prevent chronicity.[14] In the present study, the level of endotoxin in MEE from acute and chronic OME was measured quantitatively by use of a synthetic substrate. Activities of lysosomal proteases (collagenase, cathepsin B, and lysozyme) also were measured in the same MEE samples to study the relationship between endotoxin levels and lysosomal protease activity in MEE. A bacteriologic study was performed to investigate the effects of microorganisms in MEE on both endotoxin levels and lysosomal protease activity in MEE.

MATERIALS

One hundred four MEEs were collected from 85 pediatric and 19 adult patients by direct aspiration under sterile conditions after therapeutic myringotomy by use of an Ionesthetizer (Xomed, Jacksonville, Fla). Before therapeutic myringotomy, the external canal was sterilized with 70% ethanol for 5 minutes. The MEE samples were classified into four groups on the basis of a report by Senturia et al[15]:

1. Mucoid group: mucoid MEEs from 56 pediatric patients with chronic OME (4 to 13 years of age).
2. Serous group: serous MEEs from 18 pediatric patients with chronic OME (5 to 15 years of age).
3. Adult group: serous MEEs from 19 adult patients with chronic OME (31 to 82 years of age).
4. Acute group: purulent MEEs from 11 pediatric patients with acute OME (2 to 11 years of age).

Differential diagnosis was established on the basis of otoscopic findings and clinical manifestations, as judged by one of the authors (K.S.). The patients with chronic OME had been suffering from OME for more than 3 months. Adult patients with chronic OME did not have any malignant tumors such as nasopharyngeal or paranasal sinus carcinoma and did not undergo radiotherapy. All the patients with acute OME had typical clinical symptoms (otalgia and hearing loss) and local findings (redness and swelling of the eardrum). They

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TABLE 1. INCIDENCE OF BACTERIAL ISOLATION FROM MIDDLE EAR EFFUSIONS

	Positive Culture	*Negative Culture*
Mucoid	9 (25.7%)	26
Serous	2 (22.2%)	7
Adult	0 (0.0%)	2
Acute	3 (100.0%)	0
Total	14 (28.6%)	35

TABLE 2. BACTERIAL SPECIES ISOLATED FROM MIDDLE EAR EFFUSIONS

Bacteria	*No. of Isolates*
Staphylococcus aureus	4
Staphylococcus species	4
Streptococcus pneumoniae	2
Enterococcus group	1
Hemophilus influenzae	2
Branhamella catarrhalis	1

were treated with myringotomy and antibiotic therapy within several days of the onset of symptoms. Immediately after bacteriologic examination, MEE samples were well homogenized with ten times by weight of sterile saline containing 10 m*M* dithiothreitol, and centrifuged at 3,000 rpm for 10 minutes at 4°C. Clear supernatants were recovered and stored at −80°C until use.

METHODS

Bacteriologic Study. Each sample was incubated in broth agar bottles (Clinical Supply Co, Hashima, Japan) immediately after sampling and was transported to the laboratory (Tokyo Clinical Bacteriological Laboratories, Tokyo) for both aerobic and anaerobic cultures.

Assay for Endotoxin Level. Endotoxin level was measured by use of a commercial assay kit (Toxicolor Test, Seikagaku Kogyo Co, Tokyo), which contained both limulus amebocyte extract and a chromogenic substrate (Boc-Leu-Gly-Arg-pNA).[16] Before the assay, 5% perchloric acid was added to the MEE sample to remove nonspecific amidolytic activity and inhibitors. *Escherichia coli* 0111:B4 endotoxin was used as a standard.

Assay for Collagenase Activity. Hydrolytic activity of collagenase was measured with the Collagenokit CLN-100 (Maruzen Oil Biochemical Co, Tokyo). Hydrolytic activity was calculated as the amount of fluorescein isothiocyanate in the proteolyzed collagen fragments, which were measured in duplicate with a fluorometer RF-510 (Shimazu, Kyoto, Japan).

Assay for Cathepsin B Activity Including Aminopeptidase B. Hydrolytic activity of cathepsin B was measured by the method of Barrett[17] with a relatively specific methylcoumaryl-amide (MCA) peptide (Z-Phe-Arg-MCA; Protein Research Foundation, Osaka, Japan). In this assay, a sample was incubated with MCA peptide in the presence of soybean trypsin inhibitor (final concentration was 50 μg/mL). The instrument was standardized (10 μg/mL of quinine sulfate equals 25 relative fluoro units [RFU][18]). Hydrolytic activities of both collagenase and cathepsin B were expressed in RFU.[18]

Lysozyme Assay. Lysozyme level was measured by use of the Quantiplate Lysozyme Test Kit (Kallestad Laboratories, Inc, Chaska, Minn).

Lactate Dehydrogenase Assay. Lactate dehydrogenase (LDH) levels were measured by use of a commercial assay kit, LDH Neo D Eiken (Eiken Kagaku Co, Tokyo). This assay is based on the method of Wroblewski and LaDue,[19] and LDH levels were expressed as Wroblewski units (WU).

Total Protein Concentration. After each sample was diluted from 300 to 600 times with 0.067 *M* phosphate-buffered saline, pH 7.2, total protein concentration (TPC) was measured spectrophotometrically with the Protein Assay Kit (Bio Rad, Richmond, Va). Bovine serum albumin was used as the standard.

Student's *t* test was employed in the statistical analyses. The values of endotoxin, cathepsin B, lysozyme, and LDH were analyzed after logarithmic transformation.

Correlation Test Among Parameters. Correlations among the levels of the parameters (endotoxin, collagenase, cathepsin B, lysozyme, and LDH) were analyzed after logarithmic transformation in both pediatric (mucoid and serous groups) and adult OME groups.

RESULTS

The results of the bacteriologic study are summarized in Tables 1 and 2. Microorganisms were isolated from 28.6% (14/49) of the MEEs cultured, 25% of the MEEs from the pediatric groups (mucoid, serous, and acute), and none of the MEEs from the adult group. Gram-negative bacteria (*H influenzae* and *Branhamella catarrhalis*) were isolated from three MEEs.

Endotoxin Levels. Endotoxin was detected in 47.8% (9/19) of MEEs in the adult group, 55.6% (10/18) in the serous, 76.8% (43/56) in the mucoid, and all MEEs (11/11) in the acute. Endotoxin levels were 278.2±464.3 pg/mL (log value, 1.68±1.07) in the mucoid group, 70.2±109.3 pg/mL (log value, 1.04±1.02) in the serous, 36.8±53.5 pg/mL (log value, 0.82±0.95) in the adult, and 784±894.9 pg/mL (log value, 2.73±0.35) in the acute (Fig 1A). The endotoxin level in the mucoid group was significantly higher than those of the serous and adult groups ($p<.05$ and $p<.01$) and significantly lower than that of the acute group ($p<.01$). There

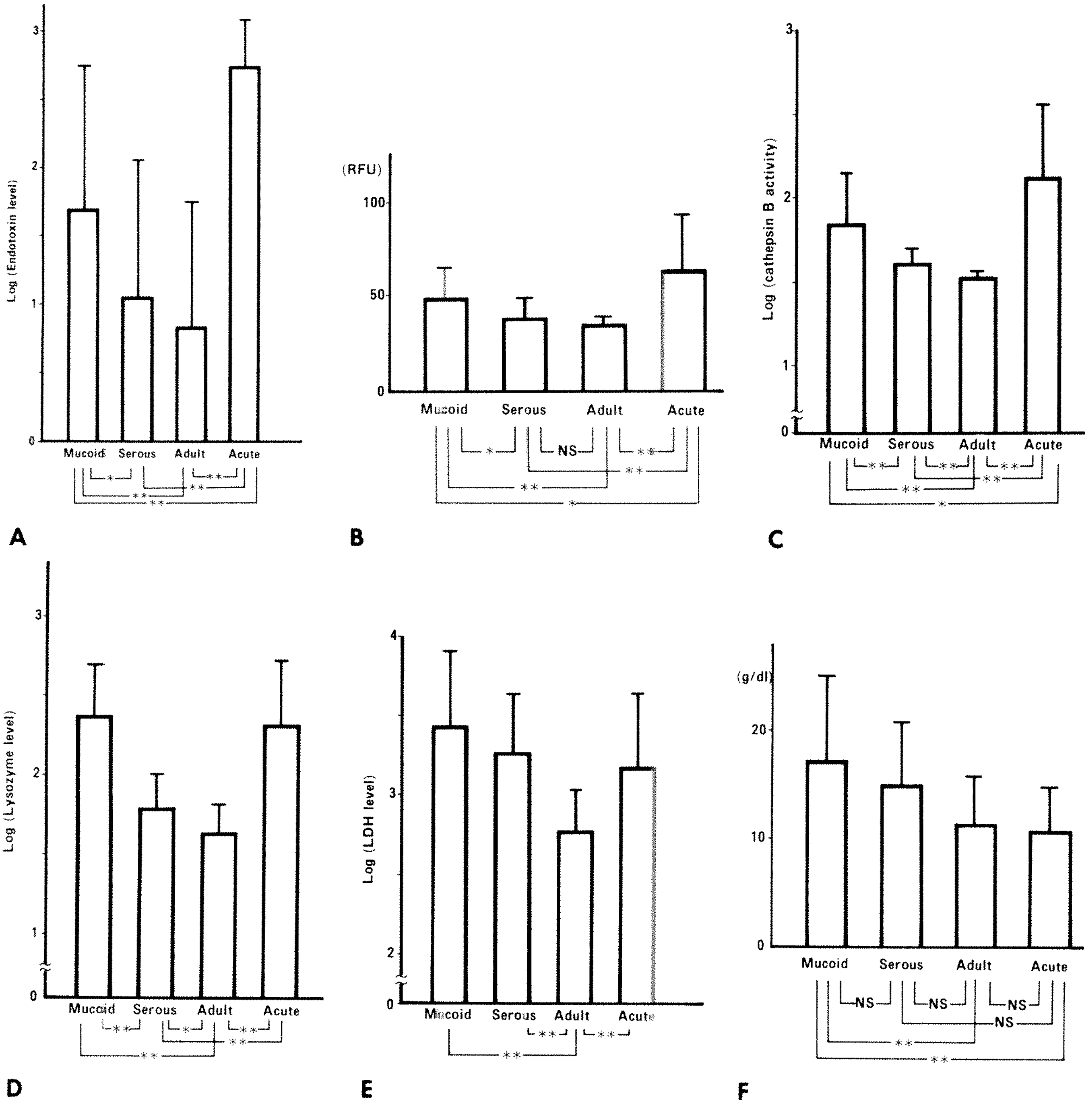

Fig 1. Findings (mean ± SD) in four groups. ✱ — significant difference (p< .05). ✱✱ — significant difference (p< .01), NS — no significant difference. A) Endotoxin levels (log-transformed data). B) Hydrolytic activity of collagenase. RFU — relative fluoro units. C) Hydrolytic activity of cathepsin B (log-transformed data). D) Lysozyme concentration (log transformed data). E) Lactate dehydrogenase (LDH) levels (log-transformed data). F) Total protein concentration.

was no significant difference between the serous and the adult groups.

Collagenase Activity. Mean values of collagenase activity were 48 ± 16.6 RFU in the mucoid group, 38.2 ± 11.4 RFU in the serous, 34.2 ± 5.1 RFU in the adult, and 62.9 ± 33.5 RFU in the acute (Fig 1B). Collagenase activity in the mucoid group was significantly higher than those of the serous and the adult groups ($p < .05$ and $p < .01$) and significantly lower than that of the acute group ($p < .05$).

Cathepsin B and B-like Thiol Protease Activity. Mean values of cathepsin B activity are summarized in Fig 1C: 94.5 ± 115.3 RFU (log value, 1.83 ± 0.31) in the mucoid group, 38.3 ± 7.8 RFU (log value, 1.59 ± 0.08) in the serous, 31.3 ± 2.3 RFU (log value, 1.51 ± 0.03) in the adult, and 214.5 ± 262.8 RFU (log value, 2.10 ± 0.45) in the acute. Cathepsin B activity was significantly different among the four groups in the following order: adult < serous < mucoid < acute ($p < .01$, $p < .01$, and $p < .05$).

Lysozyme Level. Lysozyme levels were 301.9 ± 269 μg/mL (log value, 2.36 ± 0.33) in the mucoid group, 65.5 ± 34.3 μg/mL (log value, 1.77 ± 0.23) in the serous, 44.8 ± 20.2 μg/mL (log value, 1.62 ±

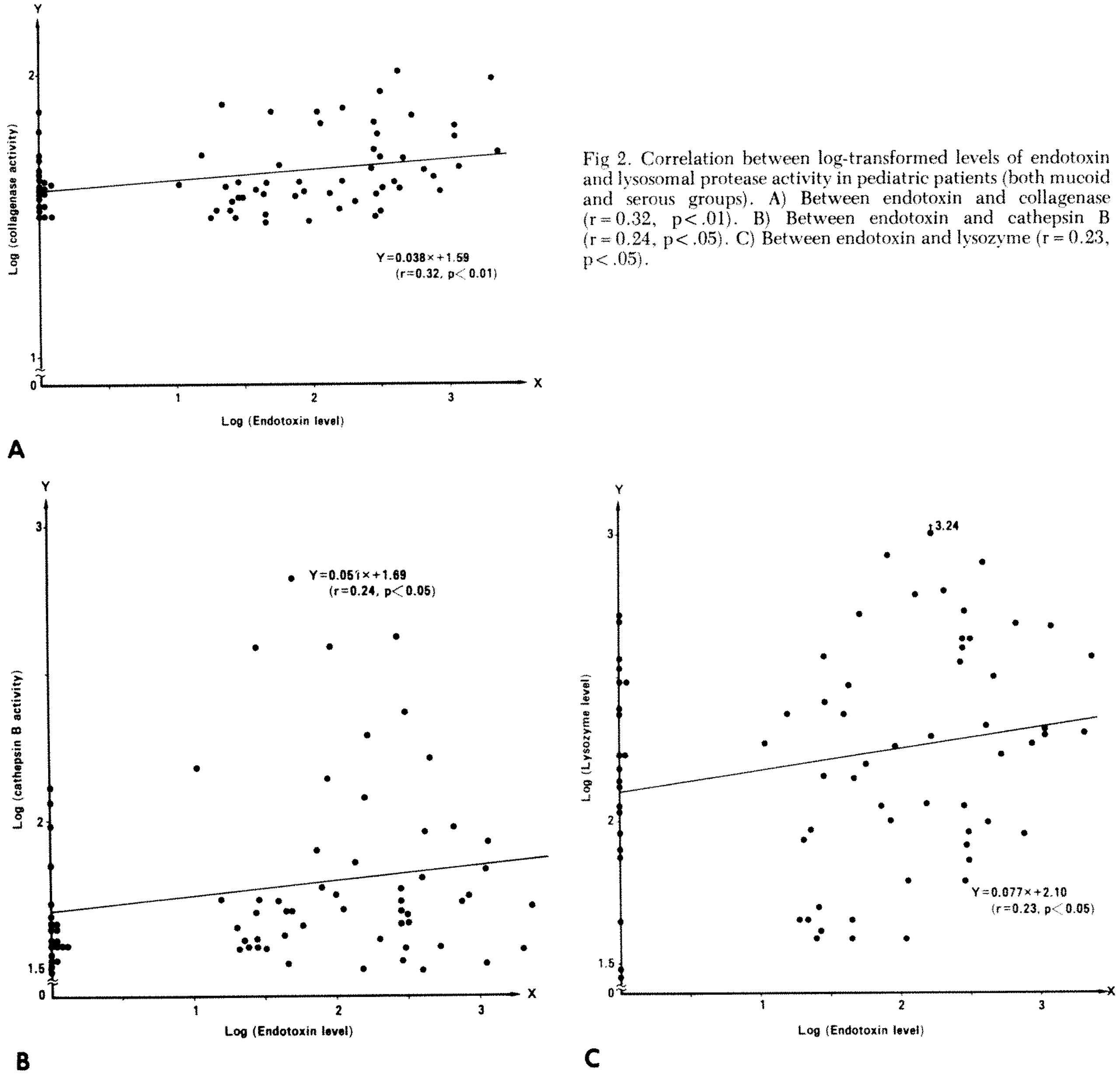

Fig 2. Correlation between log-transformed levels of endotoxin and lysosomal protease activity in pediatric patients (both mucoid and serous groups). A) Between endotoxin and collagenase (r = 0.32, p < .01). B) Between endotoxin and cathepsin B (r = 0.24, p < .05). C) Between endotoxin and lysozyme (r = 0.23, p < .05).

0.19) in the adult, and 307.2±322.2 μg/mL (log value, 2.30±0.41) in the acute (Fig 1D). The lysozyme level in the serous group was significantly higher than that of the adult group (p < .05) and significantly lower than those of the mucoid and the acute groups (p < .01). There was no significant difference between the mucoid and the acute groups.

Lactate Dehydrogenase Activity. The LDH levels were 4,414.3±4,015.2 WU (log value, 3.42±0.49) in the mucoid group, 2,465.5±1,878.3 WU (log value, 3.26±0.38) in the serous, 719.3±553.4 WU (log value, 2.77±0.27) in the adult, and 2,977.2±4,327.7 WU (log value, 3.17±0.48) in the acute. The LDH level in the adult group was significantly lower than those of the other three groups (p < .01, Fig 1E).

Total Protein Concentration. Mean values of TPC were 17.1±8.7 g/dL in the mucoid group, 14.6±6.4 g/dL in the serous, 11.4±4.3 g/dL in the adult, and 10.6±4.3 g/dL in the acute. The TPC was significantly higher in the mucoid group than in the adult and acute groups (p < .01, Fig 1F).

Correlation Among Parameters. Correlation tests between the log-transformed values of endotoxin levels and protease activity (collagenase, cathepsin B, and lysozyme) were performed. In children with chronic OME (mucoid and serous groups), a significant correlation between endotoxin level and lysosomal protease activity (collagenase, cathepsin B, and lysozyme) could be observed (r = 0.32, p < .01 in collagenase; r = 0.24, p < .05 in cathepsin B; and r = 0.23, p < .05 in lysozyme; Fig 2). On the other hand, there was no significant correlation between endotoxin levels and lysosomal protease activity in the adult group.

The levels of endotoxin and lysosomal protease

TABLE 3. ENDOTOXIN AND LYSOSOMAL PROTEASE LEVELS (MEAN±SD) IN CULTURE-POSITIVE AND CULTURE-NEGATIVE MIDDLE EAR EFFUSIONS FROM CHILDREN WITH CHRONIC OTITIS MEDIA WITH EFFUSION

	Endotoxin (pg/mL)	*Collagenase (RFU)*	*Cathepsin B (RFU)*	*Lysozyme (μg/mL)*	*Lactate Dehydrogenase (WU)*
Positive culture (n = 11)	195.1±345.4	42.3±16.3	66.6± 45.3	328.4±487.0	5,407.4±3,821.7
Negative culture (n = 33)	261.3±418.4	47.6±18.1	84.3±122.5	211.8±165.5	3,901.8±4,255.2

RFU — relative fluoro units, WU — Wroblewski units.

activity in both culture-positive and culture-negative MEE samples are shown in Table 3. There was no significant difference in endotoxin level or lysosomal protease activity between culture-positive MEEs and culture-negative MEEs.

Table 4 shows lysosomal protease activity in both endotoxin-positive and endotoxin-negative MEEs from children with chronic OME. Cathepsin B activity was significantly higher in endotoxin-positive MEEs than in endotoxin-negative MEEs ($p < .05$).

DISCUSSION

Although we could not perform bacteriologic studies on all the MEE samples, bacteria were cultured in 25% of MEEs from children with chronic OME. In culture-negative MEEs, it is difficult to conclude that there had been no bacterial infection in the middle ear. Microorganisms may have been killed by host defense mechanisms in the middle ear mucosa, or culture conditions might have been unsuitable for microorganism growth and colony formation. Since endotoxin is released from both live and dead bacteria, its level in the MEE is a more sensitive indicator of gram-negative bacterial infection than a bacterial culture test. Endotoxin is a cell wall component of gram-negative bacteria such as *H influenzae*, and has various biologic activities that cause an inflammatory reaction in the locus.[20] Endotoxin activates the complement system and is related also to the release of vasoactive amines and other mediators from leukocytes.[21] In the present study, endotoxin was detected in 47.8% of the MEE samples in the adult group, 55.6% in the serous, 76.8% in the mucoid, and 100% in the acute, and its level was ranked in the following order: adult< serous< mucoid< acute. These results suggest a high incidence of gram-negative bacterial infections in both the acute and the mucoid groups. Correlations between endotoxin levels and lysosomal protease (cathepsin B, collagenase, and lysozyme) activity were analyzed by the ratio of their levels to TPC, to minimize the influence of concentration of MEEs through long-term retention in the middle ear cavity. Endotoxin level was significantly correlated with lysosomal protease activity in MEEs from children with chronic OME. Since lysosomal proteases, especially cathepsin B and collagenase, are derived mainly from neutrophils and macrophages, endotoxin in MEEs of pediatric OME patients appears to lead to leukocyte infiltration into the locus, and to stimulate the release of lysosomal proteases and chemical mediators from leukocytes. On the other hand, there was no significant correlation between endotoxin and lysosomal proteases in adults, and endotoxin level was the lowest in adults with chronic OME, suggesting that endotoxin may not be a major factor relating to the chronicity of adult OME.

Lysosomal proteases are considered to play key roles not only in host defense mechanisms in the normal mucosa, but also in damage of the middle ear mucosa by both direct proteolysis of tissue proteins and the activation of precursor proteins (complements, plasminogen, and kininogen).[9,12]

In order to minimize the contamination of proteases released from leukocytes in MEEs after sampling, fresh MEE samples were homogenized and centrifuged to separate cellular components from MEE samples and stored at −70°C.

In children with chronic OME, only the cathepsin B fraction of total protease activity was significantly higher in endotoxin-positive MEEs than in endotoxin-negative MEEs. Cathepsin B, which is one of the lysosomal thiol proteases, is released mainly from macrophages during chronic inflammation.[22,23] Therefore, this result suggests that cathepsin B activity in MEEs may increase in the presence of endotoxin, which enhances macrophage accumulation in the middle ear mucosa with chronic inflammation. Hamaguchi et al[11,12,24] have reported the significance of cathepsin B–like thiol protease activity in the pathogenesis of chronic OME, because of its resistance against a major protease inhibitor (α1-antitrypsin) and the shortage of available thiol protease inhibitors.[11,12,24] Cathepsin B activity, among lysosomal protease activities, seems to be the most reliable index to reflect the degree of chronic OME.

TABLE 4. LYSOSOMAL PROTEASE IN ENDOTOXIN-POSITIVE AND ENDOTOXIN-NEGATIVE MIDDLE EAR EFFUSIONS FROM CHILDREN WITH CHRONIC OTITIS MEDIA WITH EFFUSION

	Collagenase (RFU)	*Cathepsin B (RFU)*	*Lysozyme (μg/mL)*	*Lactate Dehydrogenase (WU)*
Endotoxin-positive	47.4±17.4	92.9±118.6*	263.6±286.7	4,258.9±3,992.9
Endotoxin-negative	41.3±10.6	50.2± 28.4	196.1±144.6	3,136.2±2,743.6

RFU — relative fluoro units, WU — Wroblewski units.

*Significantly higher than endotoxin-negative ($p < .05$).

Collagenase is also one of the lysosomal proteases, and it is derived mainly from neutrophils, macrophages, and fibroblasts.[25] Paparella et al[26] reported that collagenase activity was higher in mucoid effusions than in serous effusions from chronic OME, and that collagenase in mucoid effusions may be produced mainly by macrophages and fibroblasts in the subepithelial spaces. In the present study, activities of collagenase and cathepsin B were ranked in the following order: adult < serous < mucoid < acute. Although cytologic studies of MEE could not be performed in the present study, this order appears to depend on the number of infiltrating neutrophils and macrophages in the middle ear mucosa and MEE.[27] In both adults and children with chronic OME, activities of these lysosomal proteases in MEE were significantly correlated with the level of LDH. Lactate dehydrogenase is a nonspecific inflammatory enzyme and originates from several sources, such as the blood, inflammatory cells, and the middle ear mucosa. Therefore, the results could be explained by lysosomal proteases' damaging the middle ear mucosa, causing breakdown of tissue proteins (collagen fibers, elastic fibers, proteoglycans, etc), and increasing the release of LDH from degenerating mucosal cells.

Lysozyme is a principal lysosomal hydrolytic enzyme and has bactericidal activity. Lysozyme in MEEs is secreted from the mucosal epithelium, neutrophils, and macrophages.[28] In the present study, the lysozyme level in the mucoid group was nearly equal to that in the acute group. Since both the number of total leukocytes and the percentage of neutrophils in MEEs are larger in acute OME than chronic OME,[29] lysozyme in the acute group is released mainly from neutrophils, while in the mucoid group, it may be released mainly from both the mucosal epithelium and macrophages.

The majority of pediatric patients with acute OME have complete resolution of any pathologic changes in the middle ear, in spite of the highest levels of endotoxin and lysosomal protease activity in MEE. On the other hand, in chronic OME, these inflammatory factors remain in the middle ear cavity for a longer period of time. Eustachian tube dysfunction due to mucosal inflammation induced by these inflammatory factors, changes in rheologic properties of MEEs,[30] and impaired mucociliary clearance[31] are major factors in retaining these inflammatory factors in the middle ear cavity.

In conclusion, endotoxin enhances leukocyte infiltration into the locus; and lysosomal proteases, especially cathepsin B-like thiol proteases, released from leukocytes, damage the middle ear mucosa and cause middle ear inflammation. The mucosal inflammation induced by this mechanism persists under the conditions of eustachian tube dysfunction, rheologic changes of MEE, impaired mucociliary clearance in the tubotympanal system, and insufficient levels of protease inhibitors against lysosomal proteases, leading to delayed recovery from acute OME in children.

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PULMONARY PARAMETERS IN CHILDREN AFTER LARYNGOTRACHEAL RECONSTRUCTION

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Laryngotracheal reconstruction in children with autogenous rib cartilage has proved successful in relieving laryngotracheal stenosis. To date, no objective measurements have been available to assess the upper airway's functional ability in these children after decannulation. A pilot study analyzing pulmonary function in 18 children successfully decannulated after laryngotracheal reconstruction was performed. The children ranged in age from 24 months to 12 years and were several months postdecannulation at the time of testing. The results of this pilot study offer an objective assessment of functional capacity after laryngotracheal reconstruction in older children and serve as a basis for objective follow-up. In younger children, pulmonary function values were difficult to obtain and proved to be of no significant value to the overall assessment of functional capacity of the airway.

KEY WORDS — children, laryngotracheal reconstruction, pulmonary parameters.

INTRODUCTION

Airway endoscopy during spontaneous breathing under general anesthesia is an accurate method of assessing the laryngeal and tracheal lumen after surgical reconstruction for treatment of stenosis. Pulmonary function studies[1] are not used to help in making the decision for decannulation. Once the patient is decannulated, further endoscopies are not indicated. However, the surgeon is always uncertain about the recurrence of stenosis. Thus, periodic assessment of the airway is usually done by repeated inquiries about the patient's clinical status and level of exercise tolerance.

To assess an upper airway, considerations should be given to physical features (the site, extent, and cause of the lesion, which in postreconstruction patients is usually known) and functional features (the character of obstruction, whether it is fixed or dynamic, and its severity). Clinical examination discloses the functional status of the patient, and airway radiographs disclose the physical condition. Direct laryngoscopy and bronchoscopy[2] usually disclose both features. However, direct laryngoscopy and bronchoscopy are invasive procedures, and once the patient has been decannulated, they should rarely be used. Direct laryngoscopy and bronchoscopy, although very accurate in assessing the severity of the stenosis, do not allow quantitative assessment of the stenosis. Pulmonary function tests — for example, flow volume loop (a graphic recording of airflow versus volume during maximal expiration and inspiration) and ratio of forced inspiratory flow at 50% vital capacity to forced expiratory flow at 50% vital capacity (FIF50/FEF50) — may be affected in a characteristic way by alterations in airway patency. Flow volume loops and FIF50/FEF50 ratio give one an idea about the site of obstruction. Other measurements, such as maximal inspiratory flow rate (MIFR), peak expiratory flow rate (PEFR), and specific airway resistance (sRAW), provide an objective quantitative assessment of the severity of the stenosis when performed correctly.

A search of the world literature for pulmonary studies of children successfully decannulated after laryngotracheal reconstruction was fruitless. The objectives of this study are 1) to check the feasibility of performing pulmonary function studies in children of different ages in a representative sample of decannulated patients after successful laryngotracheal reconstruction, 2) to study any possible correlation between physical activity and pulmonary function studies, and 3) to develop a patient data bank for baseline pulmonary flow studies for future detection of deterioration of the stenosis or possible growth of the repaired segment.

MATERIALS AND METHODS

Between October 1986 and October 1988, 28 patients underwent laryngotracheal reconstruction with costal cartilage grafts and stents at Children's National Medical Center, Washington, DC. (None of the procedures was just a cricoid split operation.) Of those 28 patients, 26 are currently decannulated. Information was obtained from pulmonary function studies, chart review, and a questionnaire completed by the parents. The majority of patients underwent laryngotracheoplasty to repair acquired subglottic stenosis following prolonged intubation related to prematurity. Two patients were intubated for a prolonged period of time following head injury, two patients had congenital laryngeal webs, and one patient suffered laryngeal trauma.

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TABLE 1. RESULTS IN SUBJECTS OVER 7 YEARS OF AGE

Case	*Age*	*FIF50/ FEF50*	*MIFR (% pred)*	*PEFR (% pred)*	*sRAW*	*FVC (% pred)*	*TLC (% pred)*	*Age Trach*	*Age Decan*	*Exercise Status*
1	12 yr 3 mo	0.55	41	52	9.8	98	85	5 yr 5 mo	12 yr	E
2	9 yr 1 mo	0.61	41	36	11.5	92	112	8 yr 9 mo	9 yr 6 mo	P
3	9 yr 7 mo	0.65	45	49	6.7	45	52	8 yr 10 mo	9 yr 1 mo	G
4	8 yr 6 mo	0.78	38	45	9.2	64	66	6 yr 4 mo	8 yr 3 mo	G
5	8 yr 7 mo	0.81	52	41	11.8	60	81	1 yr 6 mo	5 yr 8 mo	E
6	8 yr 6 mo	1.13	118	72		77		2 mo	6 yr 7 mo	E

FIF50 — forced inspiratory flow at 50% vital capacity, FEF50 — forced expiratory flow at 50% vital capacity, pred — predicted, MIFR — maximal inspiratory flow rate, PEFR — peak expiratory flow rate, sRAW — specific airway resistance, FVC — forced vital capacity, TLC — total lung capacity, Trach — at tracheotomy, Decan — at decannulation, E — excellent, P — poor, G — good.

Age at the time of the initial tracheotomy for all patients ranged from 2 months to 8 years 10 months. Patients with acquired subglottic stenosis secondary to prolonged intubation had their tracheotomy between 2 months and 10 months, with a mean of 5.6 months. The duration of time all patients spent with tracheotomy ranged from 3 months to 6 years 7 months. The age at decannulation also varied widely, from 18 months to 12 years.

Review of videotapes showed the majority of the laryngeal lesions to be either glottic-subglottic or subglottic only. Glottic-supraglottic lesions were less common, and laryngeal webs the least common. The majority of patients underwent anterior and posterior cartilage grafting with stent placement.

Following a minimum of 3 months after decannulation, 18 patients underwent pulmonary function testing. Ten younger patients were tested on a Collins 10-L Stead-Wells spirometer. All tests were performed with the child breathing into a soft-seal facemask. Eight older patients were tested on a computerized Sensomatix 10-L horizontal rolling seal spirometer. Normal values (predicted) were from Weng and Levison.[3] All tests were performed according to standard laboratory protocol. A minimum of three forced expiratory–forced inspiratory maneuvers were recorded on all patients. The best effort for the older patients was selected as the largest sum of forced vital capacity and forced expiratory volume in 1 second (FEV1). Specific airway resistance and functional residual capacity were measured on older patients in a Collins 500-L constant-volume body plethysmograph. Parameters analyzed included MIFR, PEFR, sRAW, forced vital capacity, total lung capacity (TLC), and FIF50/FEF50.

To supplement the pulmonary function tests, parents completed a questionnaire about their child's pulmonary status. They were asked whether their child had ever been diagnosed as having wheezing, asthma, bronchitis, or pneumonia. All information regarding bronchodilator medication was recorded as well. The parents were also specifically asked for their subjective assessment of the child's activity level. Exercise status was judged excellent if the child could play normally with peers, good if the child tired early during vigorous play, and poor if the child became markedly short of breath when performing simple nonstrenuous tasks.

RESULTS

Of the 18 patients who underwent pulmonary function testing, 8 more cooperative and older patients were tested with maximum expiratory and inspiratory flow volume curves. Results of six of these tests were of excellent quality. One of these 6 children was unable to perform body plethysmography for determination of airway resistance and absolute lung volume. Two sets of results were of poor quality; these patients were 5 years 8 months and 6 years 5 months old.

Of the six older children who had good test performance, five had evidence of upper airway obstruction. When FIF50/FEF50 is < 1, it is considered significant for upper airway obstruction, while ratios ≥ 1 are normal. These five children had FIF50/FEF50 < 1 (range, 0.55 to 0.81; average, 0.68). They also had a marked decrease in MIFR (range, 38% to 52% of predicted normal values; average, 43%). Finally, whereas a normal sRAW is <4.5, these five children had a marked increase in sRAW (range, 6.7 to 11.8; average, 9.8). Individual results for these children are given in Table 1.

Parent assessment of exercise tolerance was rated excellent in three children, good in two children, and poor in one child. The child with poor exercise tolerance has asthma requiring daily bronchodilator therapy. One child with good exercise tolerance has asthma and the other child has shortness of breath with vigorous exercise.

Ten children were tested via facemasks and use of tidal flow pattern evaluation. Five of these young children had good test performance. One child could not perform because of developing bronchospasm and is excluded from the results, and four children gave poor efforts. Maximal efforts were probably not obtained, but measured vital capacity establishes a minimum baseline for each child. The nine younger children plus the two older children who gave poor effort all had an FIF50/FEF50 >1. This group exhibited a 30% to 50% breath-to-breath variation in FIF50/FEF50, compared to less than 10% variation between maneuvers in the six older, more cooperative children. In this group, nine had

TABLE 2. RESULTS IN SUBJECTS 7 YEARS OF AGE AND YOUNGER

Case	*Age (yr)*	*Exercise Status*	*FVC*	*% Predicted FVC*	*FIF50/ FEF50*
7	7	E	0.49	52	1.22
8	5	G	0.77	61	1.36
9	6	E	0.45	33	1.49
10	2 yr 5 mo	E	0.54	56	1.00
11	5	G	0.22	17	1.12
12	5	E	0.58	50	1.14
13	4 yr 5 mo	E	0.78	60	1.20
14	4	E	0.43	37	1.54
15	4	E	0.39	42	2.08
16	2 yr 5 mo	E	0.32	41	1.70
17	1 yr 10 mo	E	0.39	55	2.35

E — excellent, G — good, FVC — forced vital capacity, FIF50 — forced inspiratory flow at 50% vital capacity, FEF50 — forced expiratory flow at 50% vital capacity.

excellent and two had good exercise tolerance. Individual results for the 11 children in this group are presented in Table 2.

DISCUSSION

Experience with our group of patients supports the idea that children over 7 years of age are excellent subjects for pulmonary function studies (Table 1). However, we were able to obtain data on children 7 years of age and younger (Table 2), who usually form the majority of patients with laryngotracheal stenosis. The availability of a technician trained to test children improves patient cooperation and the obtaining of pulmonary function data.

The upper airway is not a static tube; dynamic alterations in its caliber exist and offer different resistances. During inspiration, the extrathoracic lumen collapses, while in expiration it opens up more fully; the opposite happens with the intrathoracic lumen. In normal subjects, 15% to 50% of total airway resistance is accounted for by the airway from the mouth to the larynx, and during quiet breathing the resistance is about 40%.[2] In addition to poor patient cooperation in younger patients, the following factors may also lead to error through changes of upper airway resistance: resolving or ensuing upper respiratory tract infection, large tonsils and adenoids, craniofacial anomalies, and nasal obstruction from allergy and nasal septal deviation. Smith and Cooper[4] studied 19 patients with laryngomalacia in infancy who were assessed several years later with flow volume loops. All had normal expiratory loops; however, seven had abnormal inspiratory loops showing persistent low-grade supraglottic airway obstruction affecting pulmonary function studies.

Obstructive lesions can be divided into variable and fixed, depending on the ability of the airway to change its caliber in response to changes in pressure. If the airway wall is mobile and variable at the site of obstruction, extrathoracic lesions will limit inspiratory flow more than expiratory flow, causing a predominant decrease in FIF50, so the FIF50/FEF50 value is <1. The reverse will occur with variable intrathoracic obstruction, with a predominant reduction in FEF50. Airway obstruction with a fixed wall will limit both inspiration and expiration equally, since airway caliber will not change. Fixed lesions decrease FIF50 and FEF50 equally with a normal FIF50/FEF50 ratio. During quiet respiration, the pressure changes across the tracheal wall are <5 cm H_2O, which will reduce the airway caliber by 15%.[2] Increased respiratory effort in patients with airway obstruction will change the transtracheal pressure to about 20 cm H_2O, and the caliber changes by roughly 50%.[2] Also, where there is partial obstruction with low intraluminal pressure, the presence of turbulent flow such as in the larynx, subglottis, and tracheal lumen after reconstruction leads to a further decrease in intraluminal pressure from a Bernoulli effect, which is caused by acceleration of air past the narrowing. Severity of obstruction can be derived from FEV1/PEFR,[2] and a ratio >10 may indicate upper airway obstruction. However, this result depends on subject effort, and in this group of patients (children) this result was not possible. Flow volume loop assessment is a more accurate measure, because the mid-vital capacity flow ratio is obtained from a part of the flow volume curve that is relatively independent of subject effort. The ratio of FIF50/FEF50 has been shown to be particularly useful in assessing extrathoracic obstruction.[5-7]

Five of six of the older children demonstrated variable extrathoracic airway obstruction, with FIF50/FEF50<1. The severity of the obstruction is more clearly seen by looking at their very low values of MIFR (average, 43% of predicted normal values) and PEFR (average, 45% of predicted normal values), and their very high values of sRAW (average, 9.8). Caution must be used when looking at PEFR and sRAW in an asthmatic patient, as they become more abnormal when the patient is wheezing.

What seems evident from these data is these children with FIF50/FEF50 ≥ 1 could be expected to be doing very well clinically, but a ratio of FIF50/FEF50 <1 does not necessarily mean poor exercise tolerance. Balogh et al[8] studied 13 patients with burns and long-term ventilation 5 years postinjury by clinical examination, tracheal radiographs, pulmonary function tests with spirometry, and whole body plethysmography for thoracic compliance; he found tracheal stenosis in 38%. It was remarkable that after long-term ventilation, patients even after inhalation trauma (secondary to burns and gaseous fumes) had only minimal impairment of pulmonary function and physical work capacity 5 years after trauma. Du:Tu and Mangiulea[9] studied 13 patients who had central (tracheal and laryngeal) stenosis diagnosed by endoscopy. Patients underwent flow volume loops with assessment of the ratio of FEV_1 to forced inspiratory volume in 1 second, which allowed classification of the patients into three groups: six with fixed obstruction, one with variable extrathoracic obstruction, and five with variable intrathoracic obstruction. They found that the severity of obstruction (evaluated by endoscopic examination) was not related to the functional disturbances, with one patient having severe tracheal stenosis but no functional alterations.

CONCLUSION

Pulmonary function tests were performed on 18 children decannulated after laryngotracheal reconstruction for laryngotracheal stenosis. Test performance was more reliable and complete on children 7 years of age or older. Tests were of value in confirming excellent exercise tolerance and correlated poorly with poor exercise tolerance. An $FIF_{50}/FEF_{50} \geq 1$ was associated with excellent exercise tolerance, but an $FIF_{50}/FEF_{50} < 1$ did not necessarily predict poor exercise tolerance. Pulmonary function results will serve to objectively assess progression of the reconstructed area in older children as they grow. Longitudinal measurement of pulmonary function will assess whether restenosis, relative stenosis secondary to failure of growth, or normal growth of the repaired segments has occurred.

The clinical impression given by exercise tolerance remains a principal factor in the noninvasive assessment of the upper airway in all ages. While pulmonary function studies should be attempted in all children, data are usually more reliable in the older, cooperative population.

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PROSPECTIVE STUDY OF SUBGLOTTIC STENOSIS IN INTUBATED NEONATES

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Although numerous retrospective studies have attempted to investigate the incidence, etiology, and pathogenesis of subglottic stenosis, there have been few prospective studies. The retrospective studies focused initially on diagnosed cases, then drew inferences regarding incidence and causality based upon data obtained from review of patient records. In contrast, this prospective study accrued data on all neonates intubated for 48 hours or longer during the 1-year intake period. There were 195 neonates entered in the study; then 36 were excluded, leaving 159 for data analysis. Parameters assessed included age at intubation (mean, 5.7 days), duration of intubation (mean, 12.3 days), and number of times reintubated (mean, 0.79). Results of this prospective study are compared to results from previous retrospective studies.

KEY WORDS — airway compromise, endotracheal tube, intubation, laryngoscopy, neonates, subglottic stenosis.

INTRODUCTION

Many physicians involved with managing medical problems in neonates have perceived an apparent rise in the incidence of subglottic stenosis (SGS). Although published reports suggest an incidence between 1% and 9%,[1-4] there is no formal method for accruing data from neonatal intensive care units throughout the United States on prevalence and incidence of SGS. In fact, there is not even complete agreement about objective parameters requisite for the diagnosis of SGS.[5] Nonetheless, the medical literature is replete with sporadic reports about the incidence of, etiology of, and methods for managing SGS. Despite the paucity of objective data, authors speculate about causal factors. Table 1 represents a summary of potential causal factors often cited in discussions about etiology of SGS. Physicians practicing at medical centers in which SGS is encountered infrequently tend to believe that meticulous insertion and fixation of the endotracheal tube are the key factors in avoiding SGS, while physicians at centers reporting a relatively high incidence of SGS speculate about low birth weight, systemic infection, and a neonate's inherent propensity for inflammatory response as major causal factors.

Given the background of imprecise available information, we designed this prospective study to elicit information about the incidence and etiology of SGS in a population of intubated neonates.

METHODS AND MATERIALS

Original Study Design. The study was originally designed with several aims. First, by monitoring a set of specific parameters in all intubated neonates, then analyzing data in those neonates that developed SGS, a correlation would be sought between etiologic factors and the development of SGS. Second, by examining the larynx of each neonate with a flexible nasopharyngoscope immediately following extubation, then following the neonate for 6 months, we could assess the value of bedside flexible direct laryngoscopy (FDL) in predicting the development of SGS. The original aims of the study can be summarized as follows:

1. Determine the incidence of SGS in neonates intubated for 48 hours or longer.
2. Attempt to correlate various monitored parameters with the development of SGS.
3. Attempt to correlate findings on FDL immediately following extubation with development of SGS and future development of respiratory symptoms or airway compromise.

TABLE 1. POTENTIAL ETIOLOGIC FACTORS

Patient-related	Development	Gestational age, birth weight, tracheal size
	General condition	Anemia, hypoxemia, pulmonary infection, viral illness, seizures
Tube-related	Local condition	Ischemia, pressure necrosis, wound healing, infection, inflammation
	Intubation	Age at initial (hours or days), route (oral versus nasal), traumatic versus atraumatic, reintubations
	Size	2.5 mm, 3.0 mm, 3.5 mm, 4.0 mm
	Fixation method	Tape, bow, other
	Duration	Hours or days

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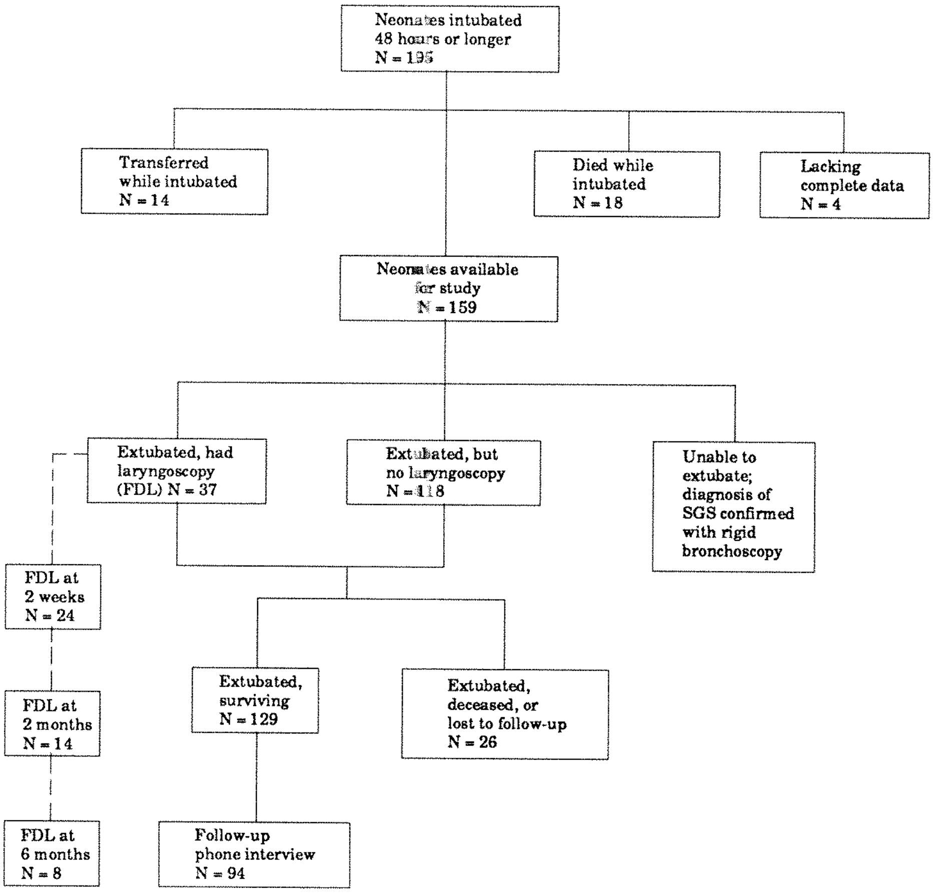

Flowchart summary of study. FDL — flexible direct laryngoscopy, SGS — subglottic stenosis.

Study Population. All neonates intubated for 48 hours or longer were eligible for entrance in the study. Excluded from the study were neonates with known congenital anomalies of the larynx or trachea. Informed consent was obtained from parents prior to performing FDL. After modifications were made in the study protocol, data were accrued on all intubated neonates that met eligibility criteria, but laryngoscopy was not performed routinely and informed consent was not obtained from parents of neonates who did not have laryngoscopy (see Discussion). The parameters assessed included birth weight, gestational age, age at time of intubation, length of time intubated, size of endotracheal tube, method used to secure tube in position, presence or absence of sepsis, ventilator settings, occurrence of seizures or hypotension, and use of steroids.

Laryngoscopy. Flexible direct laryngoscopy was accomplished as a bedside examination with use of the Olympus ENF type T flexible nasopharyngoscope with Olympus ILK-3 cold light supply. Laryngoscopy was performed with patients fully awake, and no topical anesthetic agents were used. During the brief laryngoscopy evaluations, heart and respiratory rates were monitored with state-of-the-art cardiorespiratory monitors. For some neonates, oxygen saturation was monitored with oximetry during laryngoscopy.

RESULTS

Overview. From September 1985 through October 1986, there were 195 neonates eligible for enrollment in the study. Data obtained were incomplete and not suitable for analysis for 36 enrolled neonates. The Figure provides a flowchart summary of the study. Laryngoscopy immediately following extubation was done in 37 neonates, and not done in 122 (see explanation below). Table 2 shows the number of patients available for FDL following extubation and provides a summary of the numbers of patients who actually had FDL. Of 129 neonates who were successfully extubated and with-

TABLE 2. FLEXIBLE DIRECT LARYNGOSCOPY (FDL) AFTER EXTUBATION

205 neonates intubated >48 hours, or died or were transferred while intubated
21 transferred
7 <48 hours after extubation
14 >48 hours after extubation
21 died intubated
4 lost to follow-up

159 neonates available for extubation FDL

37 neonates had FDL = 37/159 = 23%

Initial FDL <48 hours after extubation, n = 37
At 2 weeks, n = 24
At 2 months, n = 14
At 6 months, n = 8

TABLE 3. INCIDENCE ACCORDING TO POPULATION DEFINITION

	Definitions	*Incidence*
SGS	Subglottic stenosis with airway obstruction documented with rigid bronchoscopy and severe enough to require tracheotomy or anterior cricoid split	n = 3
ADM	All admissions to neonatal intensive care unit	SGS/ADM = 3/462 = 0.65%
N-INT	Neonates intubated 48 hours or longer	SGS/N-INT = 4/195 = 2.1%
N-EXT	Neonates extubated, survived, and available for follow-up	SGS/N-EXT = 3/159 = 1.9%

TABLE 4. COMPARISON OF PARAMETERS BETWEEN INFANTS WITH SUBGLOTTIC STENOSIS AND UNAFFECTED GROUPS

	No Stenosis		*Subglottic Stenosis*		
	Mean	*Range*			
Birth weight (g)	2,180.4	585-4,800	920	1,340	2,640
Gestational age (wk)	34.0	25-43	30	32	37
Age at intubation (h)	5.7	0-78	0	0	27
	No.	*%*			
Steroids					
Yes	69	45	+	+	−
No	84	55			
Hypotension					
Yes	37	24	+	+	−
No	117	76			
CPAP					
Yes	53	35	+	+	+
No	99	65			
Seizures					
Yes	16	10	+	−	+
No	139	90			

CPAP — continuous positive airway pressure. Symbols + or − indicate present or absent in each of 3 patients with subglottic stenosis.

out diagnosed SGS, follow-up information could be obtained for 94 patients 1 year after hospital discharge.

Flexible Direct Laryngoscopy Following Extubation. The original study protocol required FDL within 48 hours following extubation, then at 2 weeks, 4 weeks, 2 months, and 6 months. As shown in Table 2, only a small proportion (23%) of extubated neonates actually were examined with FDL according to the study protocol.

The reasons for not accomplishing the direct laryngoscopies as had been planned in the protocol are as follows:

1. Reluctance of parents to allow patients to have the procedure even though the minimal risk was fully explained. Parents did not want a flexible nasopharyngoscope inserted just at the time their babies were being extubated and, often, were able to be cradled in a parent's arms for the first time.
2. Logistic problems including nonavailability of a study investigator at exact times when extubation was planned or immediately following unplanned (accidental) extubation.
3. Evidence of poor interobserver reliability when the first patients entered in the study were examined by two principal investigators to test interobserver reliability.

Finally, when it was evident that the data being obtained from FDL were incomplete and questionably accurate, and that parents were reluctant to consent to FDL, a decision was made to delete from the study the requirement that enrolled patients have FDL immediately following extubation.

Subglottic Stenosis. Three neonates were judged on rigid bronchoscopy to have SGS. None of the patients with diagnosed SGS were in the group of patients who had FDL immediately following extubation. For lack of an adequate airway, two of the patients with SGS had tracheotomies, and one was successfully extubated after an anterior cricoid split operation. Neonates who died intubated did not have postmortem examinations. For the population of neonates studied, the incidence of SGS was 1.5%. Table 3 shows the various incidences according to the population considered to be at risk in this study. Table 4 compares characteristics and findings of the small group that did develop SGS with the larger group in which no SGS was detected. Two of the three neonates with SGS were intubated at birth, and they had birth weights and gestational ages lower than the average in the unaffected group. Table 5 also compares parameters, especially those related to the endotracheal tube, between the SGS and the unaffected groups. For two neonates with SGS, duration of intubation was significantly longer than in the unaffected group. A comparison is also shown for the absolute number of times each neonate was reintubated, along with a comparison of a more relative measure, ie, the number of reintubations divided by total time spent intubated on a ventilator. Since all neonates did not maintain the same size tube throughout the entire time spent intubated, a distribution is shown indicating the sizes of endotracheal tube for the first and last intubation for each neonate.

DISCUSSION

Prior Studies. The results of this study are most helpful when viewed in the context of prior published data regarding incidence and etiology of SGS. Table 6[3,5-9] provides a summary of six retrospective studies, and Table 7[4,10,11] is a summary of information to be gleaned from three prospective studies that have been reported. Flaws in study design are common to many of the studies. First, incidence is usually not reported by year, so that trends in the prevalence of SGS are difficult to discern. Al-

TABLE 5. COMPARISON OF TUBE-RELATED FACTORS BETWEEN STENOSED AND UNAFFECTED GROUPS

	Unaffected		*Subglottic Stenosis*		
	Mean	*Range*			
Duration of intubation (d)	12.3	2-93	2	21	66
Times reintubated	0.79	0-9	1	1	6
Time reintubated/time on ventilator	0.065	0-0.5	0.50	0.048	0.091
	First Intubation	*Last Intubation*	*First Intubation*		*Last Intubation*
Size 2.5 mm	19.5%	12.4%	1		0
3.0 mm	37.2%	44.2%	1		3
3.5 mm	31.9%	28.3%	1		0
4.0 mm	10.6%	14.2%	—		—
Fixed method	Tape 98%; bow 0.0%; both 1.3%; other 0.6%		Tape 3; bow 0; both 0; other 0		

though most investigators suggest an increasing incidence of SGS, descriptions of the retrospective studies tend to merge years by reporting a specific number of cases of SGS detected within the arbitrarily chosen time span. For example, when one institution is found to have nine cases over 5 years, there is not sufficient information provided to know if there were six cases in the last 2 years and one case in each of the prior 3 years, or if there was a more even distribution of the cases over the study period. Making the distinction is important; there either is or is not a trend toward the development of SGS among neonates who have remained intubated for a prolonged time. If all investigators were to report figures on incidence by stating the number of cases detected in a given population of neonates each year, then the information would be available to determine more definitively whether the trend toward a higher incidence of SGS is real or apparent.

The second problem with gaining meaningful information from published reports is the matter of the nebulous denominator. Several investigators have failed to state clearly characteristics defining the population within which the reported cases of SGS have occurred. Sometimes the population at risk is all live births, sometimes the population is neonates admitted to a neonatal intensive care unit; in other studies, the at-risk population is all neonates intubated for more than 48 hours, and in still others the study population is limited to neonates intubated for a prolonged time (more than 14 days). Until there is more consistency in defining and describing the populations being studied, it will be difficult to meaningfully interpret the significance of sporadic reports and nearly impossible to compare incidence of SGS among various institutions.

A third problem with the reporting of SGS is the matter of knowing exactly how each investigator defines and categorizes SGS. Some report SGS in categories such as "mild, moderate, and severe," while others claim that stridor and evidence of airway compromise are requisite findings. In some studies, SGS was a diagnosis made at rigid endoscopy, and in other studies SGS was a disorder defined by findings on bedside flexible fiberoptic laryngoscopy examination. The need for agreement among investigators on a standard definition and method for reporting severity of SGS has already been articulated.[4]

Determining Causality. Until investigators are able to agree upon a definition of SGS and some

TABLE 6. RETROSPECTIVE STUDIES

Authors	*Years of Study*	*Study Population*	*Comment*
Holinger et al[6]	1965-74	158 cases SGS	Acquired and congenital cases, ? denominator, ? incidence
Parkin et al[7]	1974	603 admissions, 292 charts reviewed, 18 SGS, 15 acquired SGS	Incidence = 2.4%/yr
Strong and Passy[9]	1971-75	201 patients, 88 intubated, 27 died, 5 SGS	Overall incidence = 5/201 = 2.4%; incidence in intubated neonates = 5/88 = 5.7%; data analysis shows correlation between SGS and duration of intubation, number of times reintubated, ? infection
Papsidero and Pashley[3]	1975-79	1,827 admissions, 562 intubated with assisted ventilation, 363 survived, 30 SGS	30 SGS per 1,827 in 5 yr = 8.2% per year
Schreiner et al[8]	1967-84	101 infants with chronic respiratory failure or prolonged ventilator dependency	32 SGS in 17 yr = 1.9% per year
Grundfast et al[5]	1980-85	67 SGS	? Denominator, ? incidence; author survey; no single best technique; limitation of retrospective study; need for standard reporting system

SGS — subglottic stenosis.

TABLE 7. PROSPECTIVE STUDIES

Authors	*Years of Study*	*Study Population*	*Comment*
Choffat et al[10]	1969-71	49 infants (nasotracheal), 13 no lesion, 13 minimal lesions, 21 large lesions but no distress, 2 severe SGS	2/49 = 4.1% incidence; rod lens telescope examination; "the smaller and more mature the child, the more severe and more frequent the lesions"
Fan et al[11]	1978-80?	95 infants (oral), 16 normal, 38 minor injury, 32 moderate injury, 9 significant injury (SGS, other injuries)	9/95 = 9% incidence; of five risk factors monitored, only duration and number of intubations correlated
Sherman et al[4]	1984-85?	197 infants (oral or nasal), 164 intubated 7 days, 47 died, 10 transferred, 5 refused study; ie, 102 completed study	Moderate or severe SGS, 10/102 = 9.8% incidence; factors correlating with SGS (duration of intubation, duration assisted); ventilation (number of reintubations, postextubation stridor)

SGS — subglottic stenosis.

convention for reporting severity and incidence, determination of causation will remain elusive. Table 1 lists most of the parameters mentioned by investigators as possible etiologic factors. Theoretically, the population of neonates at greatest risk for developing SGS are the low-birth weight and markedly premature newborns who would be most likely to require prolonged endotracheal intubation for mechanically assisted ventilation. In the past, investigators have shown a tendency to focus on parameters related to the endotracheal tube (size, fixation method, duration of intubation) as etiologic factors in the development of SGS rather than host systemic factors such as immune factors, inflammatory response, or tracheal size at birth. Also, there has been little consideration given to the possibility that there may be an inherently abnormal pattern of tracheal growth in the markedly premature neonate who has respiratory and circulatory impairment. A distinction does need to be made. After all, it is quite possible that the apparent increasing incidence of SGS is not a result of any parameter related to endotracheal intubation, but a sequela of prematurity. The apparent increasing incidence may be due to the improving ability to keep alive newborns who are not anatomically or physiologically developed to the stages expected at birth after 37 to 42 weeks' gestation. From this viewpoint, it seems that investigators may be attempting to attribute causality to factors that, in the end, may be found to be only supportive measures correlated more with the degree of anatomic and physiologic immaturity of the infant than with causation of SGS.

Statistical Realities. A problem encountered with this study and with prior studies reported by other investigators has been the proportion of study patients developing SGS compared with the total number of patients studied. In this study, 195 neonates were enrolled, data were usable on 159, and only 3 developed SGS. When attempts were made to correlate factors listed in Table 1 with the development of SGS, no useful correlations could be discerned. If there were fewer theoretically feasible etiologic factors and more detected cases of SGS, then statistical correlations would be meaningful. Interestingly, one of the most recent and best-designed prospective studies attempting to investigate etiologic factors for SGS also suffered from limitations of statistical analysis involving a relatively small number of index cases found within a large population in which multiple independently variable parameters are being assessed as etiologic factors. Sherman et al[4] used several different methods of statistical analysis in attempting to correlate certain risk factors with the development of SGS. Unfortunately, they used the Pearson product-moment method for identifying meaningful correlations. This method is ineffective for identifying the specific parameters associated with a dichotomous variable such as SGS. A more informative approach would have been the grouping of study patients according to presence or absence of SGS, then using two-sample *t* tests for each variable to test for differences in means between patients with and without SGS (L. Kammerman, personal communication, 1988).

SUMMARY

The prospective study has failed to yield data sufficient for achieving the aims stated in the study protocol. That is, the study did not answer the questions regarding predictive value of FDL immediately following extubation, and the factors important in the causation of SGS could not be differentiated from all of the parameters monitored. Logistic problems primarily were responsible for the failure to effectively implement the laryngoscopy aspect of the study, but the attempt to make discoveries regarding correlations with etiologic factors was thwarted more by the low number of cases of SGS occurring in the study population than by study design or implementation flaws.

Although results of the study may not be revealing in one sense, they are helpful in several ways. First, the comparison and analysis of prior studies suggest that there is little uniformity or consistency in the way in which clinical investigators have been reporting results of studies on the etiology of SGS. Consequently, the true incidence and prevalence of SGS throughout the United States have not yet been ascertained. Second, until investigators can agree on a uniform definition and/or classification system for SGS, results of all reported studies will be difficult to interpret. Third, although there have been numerous reports implicating such factors as endotracheal tube size, duration of intubation, and number of reintubations in the causation of SGS, conclusions regarding the relative causal importance of these and other factors shall have to await accrual of data from large-scale studies that are rigorously designed and implemented. Fourth, although a prospective rather than retrospective method will be more likely to yield meaningful results, a properly designed prospective study probably will require significant funding and the cooperation of investigators working at many medical centers.

CONCLUSIONS

On the basis of review of relevant literature and results of this study, conclusions that can be drawn are as follows.

1. The extent to which SGS is a *preventable* sequela of prolonged intubation in low-birth weight and prematurely born neonates is not known.
2. Probably, the cause of SGS is multifactorial and determination of causality will involve multivariate analysis.
3. The low incidence and prevalence of SGS within individual neonatal intensive care units make it difficult for each unit to accrue data sufficient to discern meaningful correlations helpful in understanding causality.
4. Further advancements in the understanding of pathogenesis of SGS are likely to come from properly designed prospective studies involving pooled data from multiple cooperating institutions.

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GLOTTOGRAPHIC ANALYSIS OF PHONATION IN THE EXCISED CANINE LARYNX

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An excised canine larynx model of phonation was developed to assess the effect of vocal fold length and tension on glottographic waveforms. The canine larynx in an experimentally produced phonatory model vibrated in a two-mass system comparable to human voice production. The recorded glottographic waveforms for the excised canine larynx were similar to signals recorded in humans in the chest register. Vocal fold length, longitudinal vocal fold tension, glottic width, and airflow rate were varied while simultaneous measurements were made of the subglottic pressure, electroglottographic signal, photoglottographic signal, and acoustic signal. The model used is illustrated and discussed, with emphasis on the method of simulating the actions of all of the intrinsic laryngeal muscles, including the thyroarytenoid muscles. The open quotient and speed quotient, calculated from the glottographic signals, were dependent on vocal fold length and tension and glottic width. These results suggest that glottographic analysis, particularly speed quotient and open quotient, provide valuable information on vocal fold vibration during phonation, and may be important in assessing laryngoplasty procedures.

KEY WORDS — electroglottography, excised larynx, laryngeal framework surgery, photoglottography.

INTRODUCTION

Laryngeal framework procedures have been developed to enable surgical improvement of the voice. A number of these procedures involve alterations in vocal fold tension, leading to changes in frequency of vibration and vibratory pattern of the vocal folds. Objective assessment of laryngeal framework surgery requires an understanding of the effect of vocal cord tension and position on voice production.

A goal of current research in laryngeal physiology is the development of valid and reliable measurements of vocal cord vibration during phonation. Standard laryngoscopic techniques allow assessment of gross neuromuscular function and anatomy of the laryngeal structures, but do not reveal the vibratory movements that actually produce voice. Photoglottography (PGG) and electroglottography (EGG) are relatively new techniques for measuring laryngeal movement.

Electroglottography measures impedance to a low current flow across the neck in the vicinity of the vocal cords.[1,2] The dynamic impedance between two electrodes over the thyroid alae changes as the vocal folds open and close, providing an estimate of vocal fold contact during the glottal cycle.[3,4] Comparison between EGG and stroboscopic investigation of the vibrating vocal folds has confirmed that the EGG signal reflects variations of lateral vocal fold contact areas.[5]

Photoglottography measures the amount of light transmitted through the vocal cords during phonation.[6] A photosensor placed on the neck below the vocal cords measures the transillumination of light through the glottis. As the vocal folds vibrate, changes in the glottal area produce proportional changes in the intensity of light transmitted. The intensity of the transmitted light during PGG has been shown by comparison with high-speed photography to be a good approximation of the cross-sectional area of the glottal aperture during phonation.[7,8]

Because PGG and EGG data reflect changes in cross-sectional area and three-dimensional configuration of the glottis, these measures allow identification of events related to opening and closing of the glottis.[8] Analysis of the PGG and EGG waveforms provides the period of the vibratory cycle. The period can be further subdivided into opening, closing, and closed portions during each cycle. Two measures of the glottal cycle with potential clinical applications that can be calculated from PGG and EGG waveforms are the open quotient and the speed quotient. Open quotient is defined as the fraction of time the cords are open during the glottic cycle. Speed quotient is defined as the duration of time the cords are opening divided by the duration of time the cords are closing (Fig 1).

Although techniques that measure glottal movements have become increasingly sophisticated, few significant applications have been made to clinical patient care. The degree to which techniques such as EGG and PGG become clinically useful will depend on how precisely the glottographic waveforms

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From the Department of Otorhinolaryngology, Mayo Clinic, Rochester, Minnesota. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Mayo Clinic.

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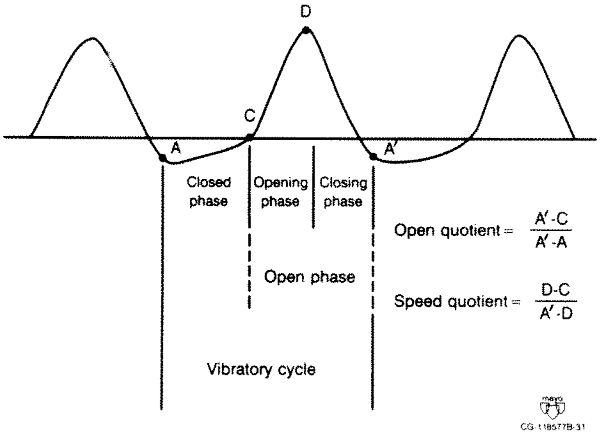
D
C
A
A'
Closed phase
Opening phase
Closing phase
Open quotient = $\frac{A'-C}{A'-A}$
Open phase
Speed quotient = $\frac{D-C}{A'-D}$
Vibratory cycle

Fig 1. Photoglottographic waveform. Period of vibratory cycle can be divided into open and closed portions, with open portion further divided into opening and closing phases. Open quotient is ratio of open phase to entire waveform period. Speed quotient is opening phase divided by closing phase. A,A' — points of initial glottal closure as lower margins of vocal folds come together, C — point of initial opening of glottis as upper margin of vocal folds separates, D — point of maximum glottic aperture.

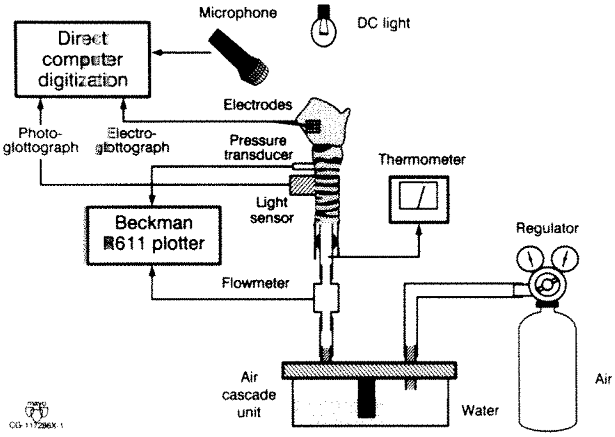

Fig 2. Schematic representation of experimental setup for in vitro laryngeal preparation.

reflect changes in laryngeal neuromuscular control. If waveform descriptors can be shown to correlate with patterns of underlying vocal fold pathophysiology, such patterns could be used to diagnose phonatory disorders and monitor treatment.

The use of animals to study laryngeal function provides a setting to test new concepts, while enabling manipulation of variables not easily controlled in humans. Traditionally, investigators have used the dog as the principal animal model on which laryngeal studies have been based.[9-11] Although the canine larynx is similar to the human larynx, there are some substantial differences in size, histology, and the configuration of the vocal folds.[11,12] Nevertheless, the excised larynx model has been an important preparation for the study of voice physiology.[13,14] The excised larynx combines the natural vibrating structure with a degree of experimental control that cannot be achieved in living organisms.[15,16]

This study involved analysis of EGG and PGG waveforms from excised canine larynges to improve our understanding of these techniques and the significance of the data obtained. The effects of variation of a number of parameters, including airflow, vocal cord tension, vocal cord length, and glottic width, on the EGG and PGG waveforms were investigated.

MATERIALS AND METHODS

SUBJECTS

The larynges were obtained from eight healthy adult mongrel dogs immediately after they were painlessly killed for organ procurement. These dogs had not undergone any previous experimental studies and had normal larynges on direct examination. The trachea was transected approximately 14 cm below the level of the cricoid cartilage. Superiorly, the incision was between the thyroid cartilage and the hyoid bone, with the soft parts cranial to the level of the false vocal folds removed.

PREPARATION AND EXPERIMENTAL DESIGN

Figure 2 illustrates the experimental method. The prepared larynx was secured to a stereotactic holder, which fixed the cricoid cartilage. A cuffed tracheotomy tube was positioned in the trachea with the cuff inflated to form a seal. The tip was 10 cm below the vocal folds and pointed rostrally. Air supplied from a compressed air canister was heated to 37°C and humidified to >95% relative humidity by being bubbled through a Bennett Cascade unit before being passed up the trachea and through the larynx. Airflow rate was controlled with a valve and measured by a pneumotachograph. The airflow meter was calibrated before every experiment by use of a Lab-Crest Flowrater.

A catheter tip pressure transducer to measure subglottic pressure was placed into the trachea between the cricoid cartilage and first tracheal ring with its tip 2 cm below the vocal folds. Calibration of the pressure transducer to 60 and 120 mm H_2O was performed before every experiment with a pressure gauge. A temperature probe was positioned at the caudal end of the trachea to confirm that the temperature of the air was maintained at 37°C.

Recording electrodes for the EGG (Synchrovoice) were sutured on each side of the thyroid cartilage, symmetrically placed. The ground electrode was secured to adjacent strap muscles. A DC light source was placed above the larynx and a Centronics OSD-2 phototransducer was fixed against the trachea just below the cricoid cartilage to record the PGG signal. The microphone for the Larson-Davis 800B sound intensity meter was mounted a radial distance of 30 cm above the glottis and off-axis to prevent direct exposure to convective airflow. To provide a flat frequency response in the

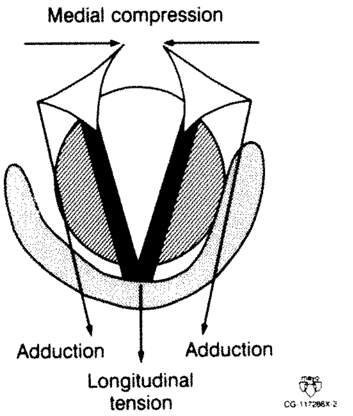

Fig 3. Longitudinal anteroposterior force on vocal folds simulates cricothyroid muscles. Lateral cricoarytenoid muscle adduction is simulated by medioventrocaudal force on muscular process of arytenoids. Interarytenoid muscle is simulated by medial compression of posterior aspect of arytenoids.

phonation spectrum with suppression of some low-frequency background noise (below 30 Hz), the C-scale of the sound intensity meter was used.

The muscular contractions of the cricothyroid muscles, lateral cricoarytenoid muscles, and interarytenoid muscle were simulated by means of surgical silk sutures (Fig 3).

Cricothyroid Muscles. Vertical and horizontal incisions were made through the thyroid cartilage to isolate a small rectangular segment of thyroid cartilage overlying the anterior commissure. A surgical silk was then sutured at one end to the anterior commissure and the incised section of thyroid cartilage. The other end of the surgical silk was attached to a force transducer (Grass FT03D). The length and tension of the vocal folds were altered by applying tension to the suture in the plane of the vocal folds.

Lateral Cricoarytenoid Muscles. The adducting force of these muscles was simulated by attaching a surgical silk to the muscular process of the arytenoid cartilage and applying force in the medioventrocaudal direction. The surgical silk, after being sutured at one end to the muscular process of the arytenoid, was passed in the medioventrocaudal direction through the paraglottic space and out the cricothyroid space just lateral to the midline. By applying tension to the sutures, the vocal folds were adducted.

Interarytenoid Muscle. A surgical silk placed through the posterior aspect of the body of the arytenoids simulated the adduction action of the interarytenoid muscle. The posterior parts of the arytenoids were thus able to be held in contact.

The most difficult of all the laryngeal muscles to simulate was the thyroarytenoid. The adductor function of this muscle was simulated in the same manner as the lateral cricoarytenoid. The problem was in the simulation of the contraction or shortening of the vocalis muscle, the inner part of the thyroarytenoid. Contraction of the medial part of the vocalis muscle would form the body of the middle part of the vocal fold, which is essential for the normal vibratory pattern of modal voice. The effect of contraction of the medial part of the vocalis muscles has been imitated only qualitatively by others.[13,15,16] In our experiment, by a technique similar to a type I thyroplasty, a piece of thyroid cartilage was excised bilaterally and a piece of Silastic was placed via this opening against the thyroarytenoid muscle. This displaced the muscle and introduced the mass necessary for the formation of the body of the vocal folds.

Controlled airflow rates, longitudinal forces, and medial forces were applied to eight excised larynges. The experiments were conducted immediately after obtaining the larynx and were completed within 3 hours. Vocal fold tension, glottic width, and airflow rate were systematically varied while the glottographic signals, subglottic pressure, and sound intensity were simultaneously recorded. Certain configurations of the larynx were retested every 45 minutes to determine if there were changes in the vibratory nature of the vocal folds over the time of the experiment.

DATA ACQUISITION

The PGG and EGG signals recorded were amplified to the ±5-V range and band-pass-filtered with five-pole Butterworth filters at 1.0 Hz and 2.5 kHz to stabilize the baseline and anti-alias for digital signal processing. The EGG and PGG signals were then low-pass-filtered at 4,000 Hz and digitized at 10,000 Hz. An AST 20868 microcomputer with an 80287 mathematical co-processor and ASYSTANT software for high-speed data acquisition and analysis were used. One second of waveform data was stored onto the hard disk of the microcomputer for later analysis.

Vocal fold longitudinal tension, airflow rate, subglottic pressure, and sound intensity were recorded simultaneously on a Beckman R611 recorder. The vocal fold length from the anterior commissure to the vocal process and the glottic width at the vocal process were measured with the aid of magnification and recorded manually.

ANALYSIS OF DATA

The glottographic waveforms were assessed to determine the mode of laryngeal vibration. The particular vibratory pattern of the vocal folds induced by the stream of air passing through the larynx depended on the configuration of the glottis. Figure 4 shows the PGG waveforms for the three vibratory modes observed. In vibratory mode 1 (Fig 4, top), the amplitudes of these low-frequency vibrations were irregular and large. This vibratory mode appeared similar to the vibratory pattern seen

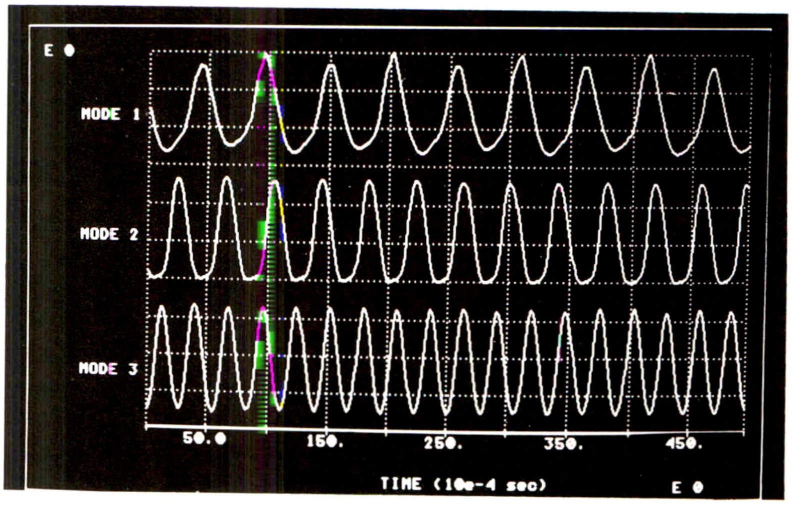

Fig 4. Photoglottographic waveforms for vibratory modes 1, 2, and 3. Amplitudes of waveforms have been normalized to 1. Vibratory mode 1 is consistent with low-frequency vibratory system similar to that seen in strohbass register. Vibratory mode 2 appears similar to two-margin modal register, consistent with chest register. Pattern of mode 3 is consistent with high-frequency pattern seen in falsetto register.

with human phonation in the strohbass or pulse register. Vibratory mode 2 (Fig 4, middle) involved a higher frequency of vibration. The vocal folds appeared to vibrate as proposed by the mucosal wave theory, with the waveform pattern similar to that observed for human phonation in the two-margin modal register. For the highest frequencies of vibration, vibratory mode 3 (Fig 4, bottom) was observed. In this mode, the PGG waveform had a regular sinusoidal pattern and appeared consistent with the vibratory mode seen for phonation in the falsetto or loft register.

Each trial of simulated phonation was classified as vibratory mode 1, vibratory mode 2, or vibratory mode 3 (Fig 4). Within each trial, a stable 0.30-second portion was chosen from the 1 second of waveform data that was recorded and stored on the hard disk. Within this segment, 10 consecutive waveforms were analyzed and averaged to calculate a single value for open quotient, speed quotient, and frequency. Data analysis and processing were performed with ASYSTANT software. Points of glottal opening and closing were determined in the manner previously described by Berke et al[11] and Childers et al.[17]

Open quotient, speed quotient, and fundamental frequency were calculated for all experimental conditions. Graphical analysis was performed to determine any changes in the above parameters with alterations of the independently controlled variables (airflow rate, vocal fold tension, and glottic width). Analysis included study of the changes in subglottic pressure and sound intensity with alterations in the vibratory mode.

RESULTS

Eight excised larynges were each studied under 70 different combinations of airflow rate, vocal fold tension, and glottic width. The frequency of vibration of the vocal folds for each larynx was varied over a range of 350 Hz. For modal-register vibration the mean frequency was 223 Hz. Throughout the experiment the specific test conditions were repeated every 45 minutes and yielded consistent results. The vibratory nature of the vocal folds was thus unchanged throughout the experiment.

When contraction of only the cricothyroid, lateral cricoarytenoid, and interarytenoid muscles was simulated, it was possible to induce vocal fold vibration in vibratory mode 1 or 3 but difficult to

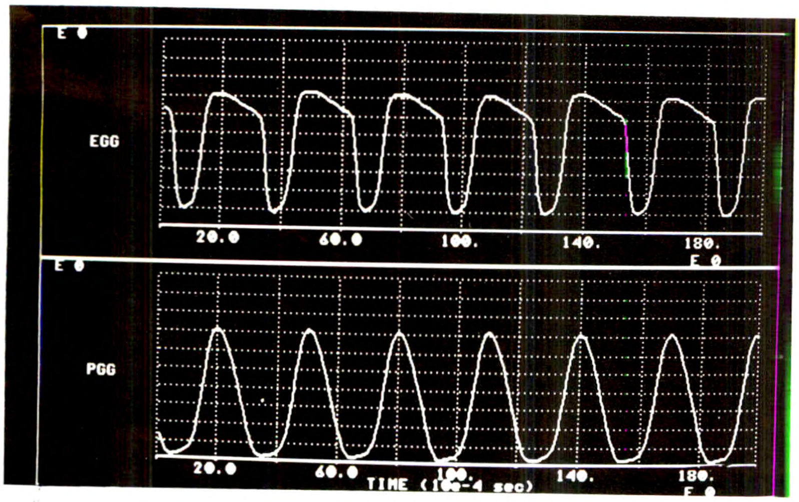

Fig 5. Simultaneous electroglottographic (EGG) (top) and photoglottographic (PGG) (bottom) waveforms for excised canine larynx with phonation in modal register (vibratory mode 2) produced by simulation of laryngeal muscles. These waveforms are similar to waveforms obtained from humans in vivo.

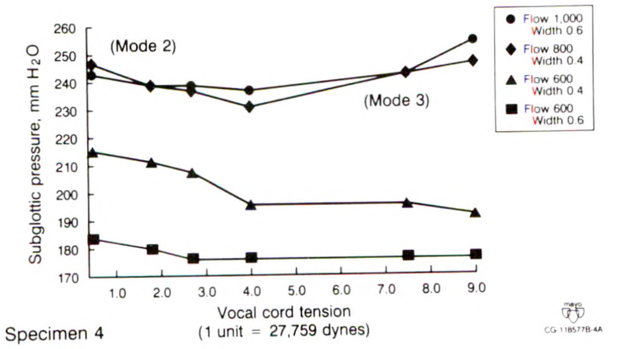

Fig 6. Subglottic pressure in relation to vocal fold tension for vibratory modes 2 and 3. Vibratory mode changes from mode 2 to mode 3 as tension increases beyond four units. Note relative consistency of subglottic pressure as tension increases. (Flow is in milliliters per second; width is in millimeters.)

induce vocal fold vibration in vibratory mode 2. By the use of Silastic blocks to increase the body of the vocal fold, vocal fold vibration in vibratory mode 2 could be produced. This finding confirmed the importance of the action of the thyroarytenoid muscle in increasing the mass of the vocal folds in the modal register. The PGG and EGG waveforms obtained for vibratory mode 2, the canine modal register (Fig 5), were similar to the waveform patterns seen in the modal register of humans.[8,11]

When contraction of the interarytenoid muscles was simulated to close the posterior part of the glottis and minimal vocal fold tension was applied, the vocal folds were loose along their borders, and when air was applied the folds slowly vibrated. The vibratory pattern of the vocal folds as shown in Fig 4 (top) was representative of vibratory mode 1, a low-frequency, one-margin system. The amplitudes of the vibrations were irregular and large. The height of the PGG wave varied from wave to wave, reflecting the irregularity of the vibratory pattern. The PGG pattern often appeared completely random.

As the vocal fold tension was increased and the vibratory mode changed from mode 1 to mode 2, the frequency and subglottic pressure increased. In vibratory mode 2 (Fig 4, middle), the larynx vibrated as proposed by the mucosal wave theory, with the thyroarytenoid muscle forming the body of the larynx and the mucosa representing the cover. For vibratory mode 2, the subglottic pressure was higher than for mode 1. Sound intensity was also greater for mode 2 than for mode 1.

Increases in tension within the modal register eventually led to a slight decrease in subglottic pressure (Fig 6). Figure 7 shows the corresponding decrease in sound intensity that occurred in the high end of vibratory mode 2. These findings were related to the abduction of the vocal folds and decreased amplitude of vocal fold vibration with increased cricothyroid tension. Decreases in glottic width increased the frequency, subglottic pressure, and sound intensity.

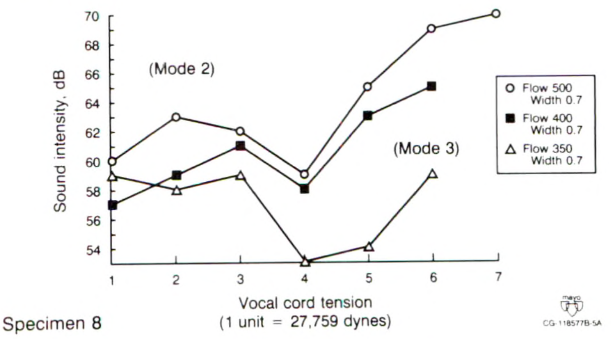

Fig 7. Sound intensity in relation to vocal fold tension. Vibratory mode changes from mode 2 to mode 3 as tension increases beyond four units. Note nonlinear relationship tension has with sound intensity in these vibratory modes. (Flow is in milliliters per second; width is in millimeters.)

With maximal stretching of the vocal fold ligaments, the vibratory mode changed from mode 2 to mode 3 (Fig 4, bottom). The PGG waveform had a small amplitude and appeared similar to a sine wave. When the vocal folds were made very long, stiff, and thin, the pitch rose and the vibratory mode changed. In vibratory mode 3, the vibrational pattern was determined by the margins of the vocal folds, and not by their body.

The increase in tension that caused the vibratory mode to change from mode 2 to mode 3 led to a rise in subglottic pressure and sound intensity. Further increases in tension led to a logarithmic rise in subglottic pressure and sound intensity until a plateau was reached (Figs 6 and 7). The plateau occurred because the vocal folds were so tense that further increases in subglottic pressure and sound intensity had to be produced by increasing the airflow.

With respect to frequency of vibration, as the vocal fold tension increased and the vibratory mode changed from mode 1 to mode 2 and then to mode 3, the pitch consistently rose (Figs 8 and 9). There was an average of 4.2 mm of actual lengthening of the vocal folds in passing from the lowest pitches to the highest pitches. The vocal folds did not lengthen proportionally with the increased tension, with little increase in length in vibratory mode 3. The relationship vocal fold tension had with frequency was not affected by the vibratory mode of phonation.

The open and speed quotients were calculated from the glottographic waveforms for the canine modal register, vibratory mode 2. The data showed a direct relationship between vocal fold tension and the open quotient in all eight dogs (Fig 10). Increases in tension within the modal register revealed no apparent effect on the speed quotient. Alterations in glottic width did affect both the open and speed quotients. Glottic width had a direct relationship with open quotient. The speed quotient was inversely related to the glottic width at the vocal pro-

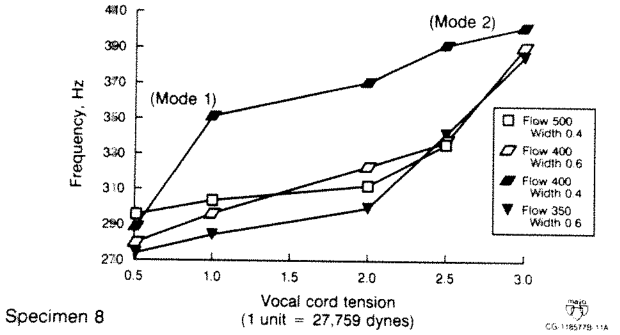

Fig 8. Vocal fold tension versus fundamental frequency. There is direct relationship between tension and frequency. For tensions of 0.5 units, larynx was in vibratory mode 1, as opposed to vibratory mode 2 for greater values of tension. (Flow is in milliliters per second; width is in millimeters.)

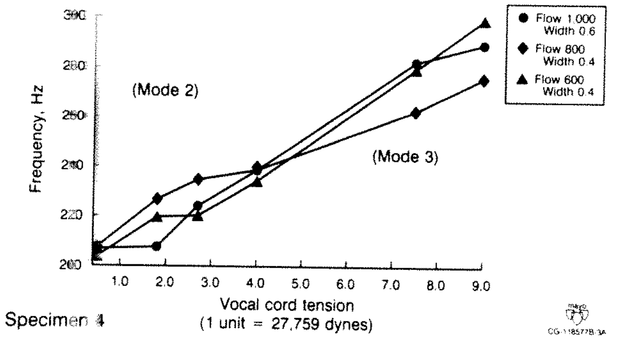

Fig 9. Fundamental frequency as function of vocal fold tension. Vibratory mode changes from mode 2 to mode 3 as tension increases beyond four units. Note direct relationship tension has with frequency. (Flow is in milliliters per second; width is in millimeters.)

cess. A decrease in glottic width increased the proportion of time the folds were opening compared to closing.

DISCUSSION

The excised canine larynx model served as a physiologic model for studing the effects of vocal fold tension, glottic width, and airflow rate on the vibratory pattern of the vocal folds. To simulate the action of the vocalis muscle, Silastic blocks were used to increase the body of the vocal folds, much the same as in a type I thyroplasty.[18]

The canine larynx, in an experimentally produced phonatory model, vibrated in a two-margin system and thus appeared comparable to human voice production.[17] The recorded glottographic waveforms from experimentally produced phonation in the canine model were similar to signals recorded from humans. The reproducibility of the vibratory pattern under specific test conditions repeated throughout the experiment confirmed the consistency of the vibratory nature of the vocal folds.

The vibrations of the vocal folds were determined by the mechanical properties of the folds and by the nature of the airflow through the glottis. Vibratory mode 1 was a low-frequency, one-margin system consistent with strohbass or pulse vocal register. The folds were approximated but loose along their borders and these relaxed vocal folds were thrown into vibration when air passed through the glottis. The glottis was not closed, or only shortly, during the vibratory cycle.[13] Each waveform cycle was usually different from the preceding cycle, reflecting the different extent of glottic opening and closing.

In vibratory mode 2, which was the modal register, the vibratory patterns were determined by the body of the vocal folds and the mucosal margin. The vocal folds exhibited a wavelike movement that consisted of vertical and horizontal components.[14]

Vibratory mode 3 was a high-frequency, one-margin system consistent with falsetto or loft vocal register. The long, stiff, and thin vocal folds vibrated with small amplitudes and no or negligible closure of the glottis during the cycle.[13] The vibratory pattern was determined by the margins of the vocal folds and not by the body of these vocal folds. These margins behaved similarly to strings, vibrating in a one-mass model. The PGG waveform showed a sinusoidal-like wave, similar to the vibrational pattern of a string. Also, the pitch was controlled by regulating the length of the vocal folds actually in vibration, the same way the frequency of vibration of a string can be regulated.

In this experimental model, glottography was necessary to distinguish the vibratory mode. It was important to be able to distinguish between the different vibratory modes in order to isolate the effects of longitudinal vocal fold tension within a given mode from the effects of changes in vibratory mode. Within vibratory mode 2, these was a logarithmic falloff in subglottic pressure and sound intensity explained in part by the abduction caused by increased longitudinal vocal fold tension. With a further increase in tension, the vibratory mode changed to mode 3 and the subglottic pressure and sound intensity increased before reaching a plateau.

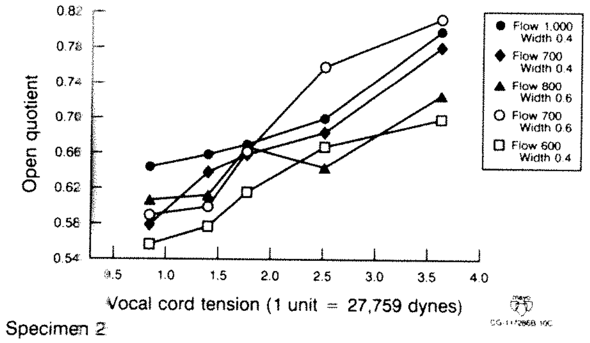

Fig 10. Open quotient as function of vocal fold tension for four configurations of glottic width and airflow rate in excised canine larynx. There is direct relationship between vocal fold tension and open quotient. These measures are for vibratory mode 2, canine modal register. (Flow is in milliliters per second; width is in millimeters.)

Thus, the effect of increased tension on subglottic pressure and sound intensity was different for each vibratory mode.

CLINICAL APPLICATIONS

During this experiment, glottic width and vocal fold tension were altered. As is known, similar alterations in glottic width and longitudinal tension of the vocal folds are made in laryngeal framework procedures. Analysis of the experimental glottographic data revealed the direct relationship tension had with frequency and open quotient in the canine larynx. The decrease in proportion of time the glottis was closed during each vibratory cycle with increased tension was related to the tense, less compliant folds' vibrating faster and spending a decreased amount of time in the closed phase. The increased tension within the canine modal register did not appear to affect the relationship of opening phase to closing phase (the speed quotient).

Glottic width had a direct relationship with open quotient and an inverse relationship with speed quotient. The effect of glottic width on subglottic pressure was responsible for these changes in vibratory pattern. With the increase in subglottic pressure, the subglottal space was pushed a greater distance upward and outward, with the glottal mucosa extended more than for lower pressures.[19] The vocal folds became very stiff during their increased excursion and snapped back to close the glottis.

The glottographic quotients from canine modal register vibration thus reflected changes in glottic configuration. The data suggest that the open quotient provided an estimate of vocal fold tension. Furthermore, valuable information on vocal fold vibratory mode and vibratory pattern during phonation could be provided by glottographic analysis. Therefore, glottography may be beneficial in laryngoplasty procedures to objectively assess the changes in vocal fold vibratory pattern produced with the alterations in vocal fold length and tension.

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CADAVER MIDDLE EARS AS MODELS FOR LIVING EARS: COMPARISONS OF MIDDLE EAR INPUT IMMITTANCE

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In vitro measurements of the middle ear input immittance in temporal bones extracted from human cadavers were directly compared with similar in vivo measurements from clinically normal subjects. The results of this comparison indicate that most otoscopically normal unfixed cadaver ears have middle ear input immittances that are indistinguishable from those of live subjects in the 0.1- to 2-kHz range — as long as they have been kept from drying and the static pressures on either side of the tympanic membrane are equal. The effects of the middle ear muscles on the measured input immittance are generally small and the cadaver ears can be maintained in the frozen state for several months with little change. Tympanometry appears to be a reliable indicator of normal middle ear immittance. Cadaver middle ears are useful models of human middle ear function.

KEY WORDS — middle ear function, tympanometry, use of cadaver ears.

INTRODUCTION

The middle ears of temporal bones extracted from human cadavers are often used both to elucidate the function of the human middle ear and as models in tests of middle ear reconstructive procedures.[1-6] However, the degree to which cadaver middle ears replicate the mechanical function of living middle ears is not well established. One measure of mechanical response that allows direct comparison between living and cadaver ears is the acoustic input immittance of the middle ear. "Immittance" is a general term that refers to either impedance or its inverse, admittance.[7] In this study we will quantify the immittance as an acoustic impedance defined by the ratio of the pressure and the acoustic volume velocity at the tympanic membrane. Since impedance is determined for tonal stimuli, it has both a magnitude and an angle that represents the phase difference between the pressure and the volume velocity.[7]

Early comparisons of impedance measured over a broad frequency range in living and cadaver middle ears[8-10] pointed out large differences between the two (Fig 1[8-11]); the magnitude of the impedance in the cadaver ears was 3 to 10 times larger than that in living ears. In contrast to these early studies, later work revealed that tympanograms taken at low frequencies in fresh cadaver ears are similar to those from normal living ears.[12-14] These tympanometric studies also suggested that in order to maintain normal middle ear function in cadaver material, care had to be taken to both ventilate the middle ear and keep it moist — precautions not taken in some of the previous studies.[8,9] Although the tympanometric studies indicated similar impedances in cadaver and normal living middle ears at the tympanometric frequencies, it is possible that large differences between the impedance in living and cadaver ears occur at other frequencies at which different structural components influence the impedance.

Several investigators have performed extensive in vitro measurements of ossicular motion in the middle ears of extracted temporal bones.[1-5,15,16] These studies suggest that fresh middle ears from cadaver temporal bones function qualitatively like the middle ears in live animals and humans. Moreover, it has been shown that such in vitro preparations can be maintained for days with little change in ossicular motion.[16] Unfortunately, direct comparisons between these in vitro measures and ossicular motion in living middle ears are not possible, since few in vivo measurements exist.

In this paper we report broadband in vitro measurements of middle ear input impedance in fresh and thawed temporal bones and compare these measurements with in vivo measurements made with similar instruments in normal ears. The effects of

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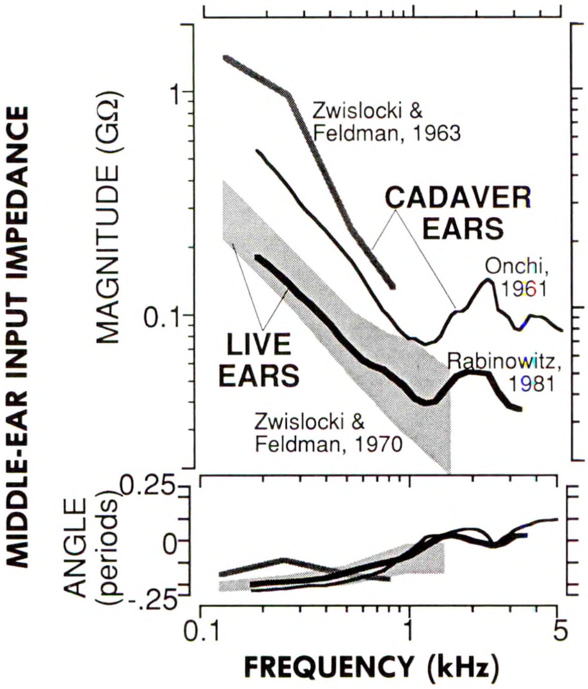

Fig 1. Comparisons of reported measurements of middle ear input impedance in live and cadaver ears. Cadaver data from Onchi[8] and Zwislocki and Feldman[9] are median impedances in 4 and 13 cadaver ears, respectively. "Live" data from Zwislocki and Feldman[10] represent 10th through 90th percentile range of impedance of 33 subjects with normal hearing, and data from Rabinowitz[11] are median impedances from four young males with normal hearing. Units of impedance are meter-kilogram-second acoustic gigaohms, where 1 GΩ = 1 Pa − s/mm³ = 10⁹ Pa − s/m³.

freezing, of the middle ear muscles, and of postmortem time on the input impedance are also reported. Since it was not possible to determine the magnitude of early postmortem changes in our temporal bone population, we also describe measurements of the middle ear impedance in animals before and after death.

METHODS

ACQUISITION, PREPARATION, AND STORAGE OF TEMPORAL BONES

An oscillating (Stryker) bone plug saw (3.8 cm in diameter) was used to obtain temporal bone ear plugs from refrigerated (3°C) human cadavers within 48 hours after death.[17] A typical ear plug included the entire bony external canal, middle ear, inner ear, and internal auditory canal and part of the mastoid and cartilaginous external canal. Extracted ears were either immediately prepared for impedance measurements or wrapped in wet gauze and stored in a freezer at −10°C to −15°C. The tympanic membranes of all of the ears appeared normal under otoscopic observation. Standard clinical 0.22-kHz tympanograms performed prior to preparation revealed that 12 of the 15 ears used in the study had static acoustic impedance values within the normal range,[18,19] while three middle ears (ears C, G, and OC of Fig 2 and Table 1) were more impedant than normal. Three other ears, with "flat" tympanograms, were excluded from further study.

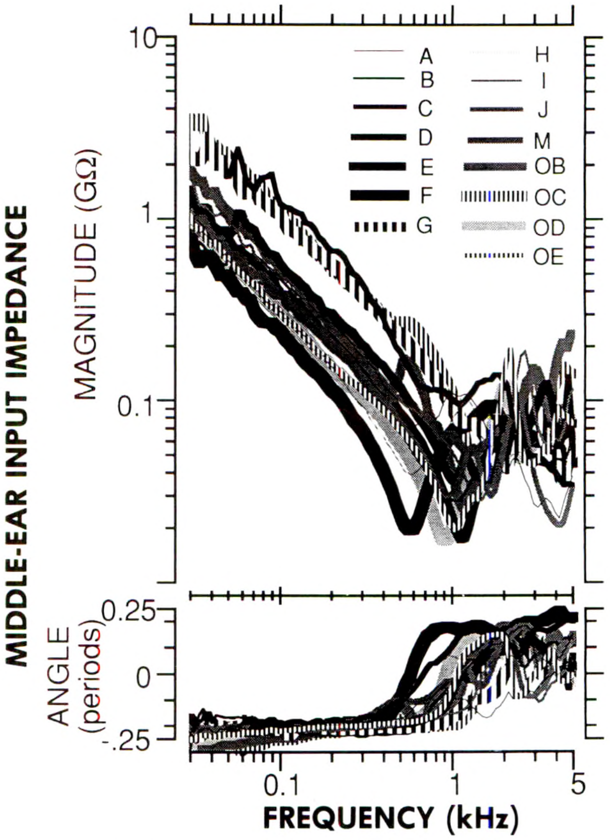

Fig 2. In vitro measurements of middle ear input impedance from 15 cadaver ears. Three ears (C, G, and OC) had peaked tympanograms with abnormally low static compliances.

Preparations for impedance measurements included shortening the ear canal in order to minimize the contribution of the ear canal space to the measured impedance. Such a procedure was considered desirable since one limit on the accuracy of middle ear input impedance measurements has been uncertainties regarding the effect of the ear canal space on the measured impedance.[11] The shortening was accomplished by removing the cartilaginous external canal and drilling away the bony canal until only a narrow rim of bone (about 1 to 2 mm) remained around the tympanic annulus (Fig 3[11,20]). During drilling, care was taken to keep the tympanic membrane and cavity intact; however, the most lateral and anterior portions of the mastoid were often removed. After the external ear was shortened, a brass annulus (14 mm outer diameter, 5 mm inner diameter, and 2 mm thickness) was centered over the umbo and fixed in place with a carboxylate cement (Fig 3[11,20]). The annulus enabled rapid and reproducible placement of the impedance measurement system.

During the impedance measurements, the middle ears of the fresh or thawed temporal bones were

TABLE 1. FEATURES OF MIDDLE EAR INPUT IMPEDANCE IN 15 CADAVER EARS

Ear	*Magnitude at 0.2 kHz (GΩ)*	*Angle at 0.2 kHz (periods)*	*Magnitude at 3 kHz (GΩ)*	*Angle at 3 kHz (periods)*	*Magnitude at Minimum (GΩ)*	*Frequency at Minimum (kHz)*	*Age at Death (yr)*	*Post-mortem Time* (d)*
A	0.27	−0.19	0.028	−0.07	0.074	0.61	17	12
B	0.20	−0.20	0.043	0.08	0.029	1.04	59	4
C	0.67	−0.18	0.050	0.17	0.095	1.05	72	16
D	0.31	−0.20	0.085	0.12	0.038	1.38	?	<100
E	0.22	−0.23	0.077	0.09	0.018	1.14	62	140
F	0.12	−0.21	0.060	0.20	0.020	0.57	63	1
G	0.58	−0.21	0.101	0.06	0.043	2.00	?	1
H	0.15	−0.19	0.062	0.09	0.040	0.58	73	1
I	0.25	−0.22	0.097	−0.08	0.029	1.43	82	1
J	0.20	−0.22	0.043	−0.08	0.030	1.68	76	1
M	0.21	−0.19	0.155	0.10	0.053	1.30	68	2
OB	0.26	−0.23	0.138	0.13	0.026	1.21	?	>300
OC	0.54	−0.23	0.111	0.12	0.035	1.48	?	>300
OD	0.15	−0.22	0.058	0.06	0.017	0.93	?	>300
OE	0.16	−0.21	0.043	−0.01	0.019	1.06	?	>300

All magnitudes are in units of meter-kilogram-second acoustic gigaohms (10^9 ohms), and impedance minimum is defined as lowest magnitude measured between 0.3- and 2-kHz range.

*Time between death and impedance measurement.

kept moist by periodic application of normal saline to the external surface of the tympanic membrane. The ear canal was rinsed with saline and then gentle suction was used to remove all excess fluid. This procedure was essential to reverse small increases in low-frequency impedance that resulted as the bone dried. The middle ear pressure in these ears was normally maintained at ambient levels via the mastoid air cells that were opened to the outside by the Stryker saw. However, in one ear communication between the middle ear air space and the outside was occluded by bone dust and debris, and time-varying pressure differences across the tympanic membrane (monitored by a shift in the peak pressure of the tympanogram) were observed. Drilling to open the mastoid prevented buildup of these pressure differences.

In nine ears repeated measurements of the input impedance were performed over a period of several months. Between measurements the ears were wrapped in moist gauze and aluminum foil and stored in a freezer. In six ears the effects of the middle ear muscle attachments on the input impedance were determined by measurements made before and after sectioning their tendons. The stapedius tendon was cut via a posterior tympanotomy approach, while the tensor tympani tendon was cut at the manubrium after wide opening of the eustachian tube.

IMPEDANCE MEASUREMENT METHODS

The methods for determining the input impedance are essentially those of Møller[20] and Rabinowitz[11] and have been detailed elsewhere.[21,22] Briefly, the acoustic source — whose volume velocity output was calibrated against known acoustic loads — was used to determine the impedance near the tympanic membrane from sound pressure measurements made over the 0.03- to 0.5-kHz range (measurement density of 40 points per decade). Repeated measurements of known impedances demonstrated that within the 0.1- to 5-kHz range the acoustic source was capable of determining the absolute impedance of the human ear with an error of less than 20% in magnitude and 0.02 periods in angle. Furthermore, measurements of the impedance of the cadaver ears were very repeatable as long as the ears were kept moist by periodic rinsing of the external canal with normal saline; over a span of a few

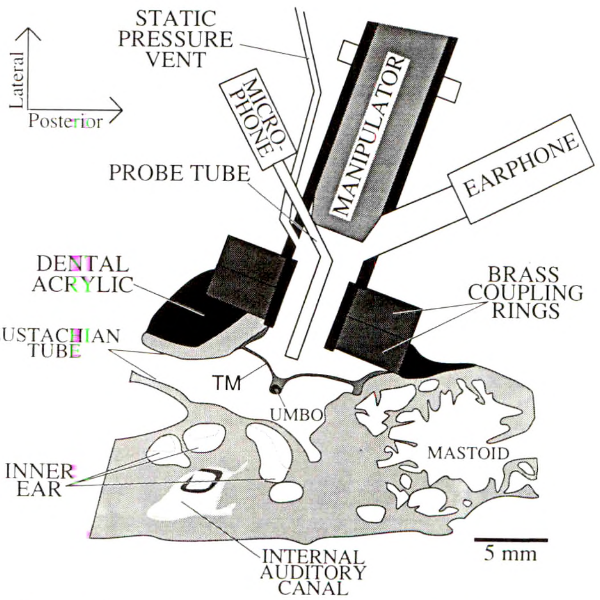

Fig 3. Schematic cross section through extracted temporal bone, showing prepared middle ear and placement of acoustic source. Medial brass ring is attached to prepared ear canal with dental acrylic. Lateral ring is part of acoustic source. Thin layer of modeling clay between two rings seals source in place. Source is constructed around standard hearing aid microphone and receiver (Knowles Corp) and is conceptually similar to sources used by Møller[20] and Rabinowitz.[11] Static pressure vent maintains ear canal pressure at ambient levels, yet is narrow and long enough that it does not significantly affect acoustic measurements.

TABLE 2. TIME CONSTANT ANALYSES OF POSTMORTEM CHANGES IN IMPEDANCE OF NINE CADAVER EARS (TIME REQUIRED FOR ORDER OF MAGNITUDE CHANGE)

	Feature			
Results of Temporal Analysis	*Magnitude at 0.2 kHz*	*Magnitude at 3 kHz*	*Magnitude at Minimum*	*Frequency at Minimum*
Shortest time constant	1,053 days	296 days	127 days	110 days
Median time constant	∞	∞	∞	∞
No. of ears with significant change	2	2	4	2

Time constants are determined by least-squares exponential fit to data such that $\log 10(x) = \log 10(a) + \text{postmortem time}/\tau$.

In this equation, τ is time constant, or time required for x to change by one order of magnitude. Significance of each time constant was determined by F test of percent variance explained by regression. Time constants that were not significant at 10% level are indicated by ∞.

hours the impedance varied by less than 10% in magnitude and 0.01 periods in angle.

Since the acoustic source was not located precisely at the tympanic membrane in these studies, the measured impedances included the influence of the residual ear canal space. The impedance of this space is inversely proportional to its volume. The residual ear canal volume was estimated in each ear by repeatedly filling the canal with tap water or saline from a calibrated microsyringe. In the 15 ears, these ear canal volumes varied between 0.1 and 0.5 mL. The small size of the remaining canal allowed us to accurately approximate the effects of this air space with an acoustic compliance in parallel with the middle ear input impedance,[10] such that

$$(1) \qquad Z_{ME} = \frac{1}{\dfrac{1}{Z_{MEASURED}} - j\,\dfrac{2\pi f V}{p0c^2}}$$

$Z_{MEASURED}$ is the complex impedance measured by the source, j is $\sqrt{-1}$, f is frequency, V is the volume of the remaining ear canal air space, $p0$ is the density of air, c is the speed of sound in air, and Z_{ME} is the calculated middle ear input impedance at the tympanic membrane.

GUINEA PIG MEASUREMENTS

The input impedance of six guinea pig middle ears was repeatedly determined during a time period immediately before and after death. The guinea pigs were deeply anesthetized throughout the procedure. A tracheal cannula was inserted, the middle ears were widely opened via a posteroventral surgical approach, and the ear canals were resected at the opening of the bony meatus. The acoustic source was tightly coupled to the narrow bony meatus by way of a nylon adapter and petrolatum, and the input impedance at the opening of the meatus was measured repeatedly for 30 to 60 minutes. The exposed trachea of the anesthetized animal was then clamped, and postmortem impedance measurements were performed periodically over the next 2 to 14 hours.

RESULTS

MIDDLE EAR INPUT IMPEDANCE OF CADAVER EARS

The results of measurements of the input impedance of 15 temporal bone middle ears are pictured in Fig 2. The Figure illustrates both variability and similarity among all of the individual measurements. In each ear the impedance magnitude varies by a factor of 40 in a frequency-dependent manner over the 0.03- to 5-kHz frequency range, while at any one frequency the impedance magnitudes of the different ears vary by a factor of 5 to 6. At frequencies below 0.4 kHz all of the impedance magnitudes are approximately inversely proportional to frequency and the angle of all the impedances is between −0.15 and −0.25 periods. This behavior is consistent with stiffness domination of the middle ear at low frequencies. In the 2- to 5-kHz region the angle of the impedance varies from masslike (0.25 periods) to resistancelike (0 periods), and there is no consistent frequency dependence observed in the magnitudes. In the middle frequencies, many of the impedance magnitudes go through a well-defined minimum at which the angles go through zero; these characteristics define a resonant frequency. Several features of the impedance measurements from each ear are listed in Table 1 along with the age of the donor at the time of death and the interval between death and the impedance measurement. No statistically significant correlation was found between any of the impedance measures and either age or postmortem time.

CHANGE IN IMPEDANCE OVER TIME

In nine of the cadaver ears measurements of the impedance in thawed ears were repeated over several months. In most ears, the impedance magnitudes and angles did not vary significantly with postmortem time (Table 2); however, in a few ears small but significant alterations in the magnitude and angle of the impedance accrued over a period of months. The direction of these small changes was inconsistent from bone to bone. There was also a tendency for the frequency of the impedance minimum to shift with increased postmortem times, usually upward (Figs 4 and 5).

EFFECT OF FREEZING AND THAWING

The effect of freezing and thawing on the impedance was ascertained by comparing the impedance of three fresh ears prepared within 24 hours of death with the impedance measured after freezing

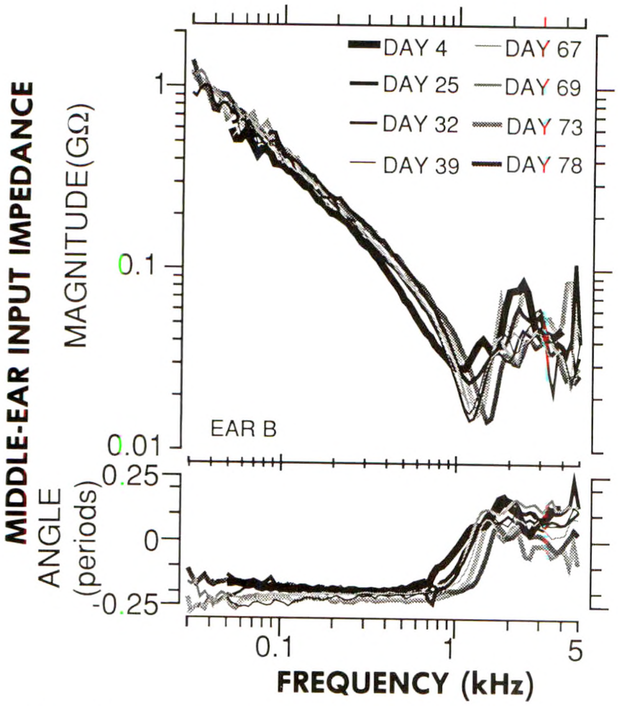

Fig 4. Eight in vitro input impedance measurements made in same cadaver ear over period of 74 days. Key notes days postmortem of each measurement. Largest changes occur near impedance minimum at time of 32-day measurement.

for several days and thawing (Fig 6). The changes produced by freezing were generally less than 40% in magnitude and 0.05 periods in angle. Some of the larger changes apparent between 0.8 and 2 kHz can be interpreted as changes in the resonant frequency of the impedance, but unexplained changes also occurred at higher frequencies in ears I and J. The changes in ear H were uniformly small at all frequencies.

EFFECT OF MIDDLE EAR MUSCLES

The effect of the middle ear muscles on the input impedance was determined by measurements made before and after sectioning both the stapedius and tensor tympani tendons in six bones at long postmortem times (>200 days). The changes in the impedance produced by these procedures were generally less than 50% in magnitude and 0.05 periods in angle (Fig 7). The largest changes in any bone usually occurred near 1 kHz and again resulted from a change in the resonant frequencies of the ears.

IMMEDIATE EFFECT OF DEATH ON MIDDLE EAR MECHANICS IN ANIMALS

Repeated measurements of impedance were made on six guinea pig ears for a period of 30 to 60 minutes before death and for 2 to 14 hours after death. In all of the ears the impedance magnitude stayed relatively constant (within 40%) after death for a period of 2 hours. Following this time a large (factor of 3) increase in the impedance occurred in five ears. These increases were all associated with some technical difficulties in keeping the middle ear moist. In one ear, the magnitude of the impedance remained relatively unchanged for 14 hours after death (Figs 8 and 9). The temporal bone was then removed from the head. The impedance of the extracted middle ear was quite similar to that of the premortem control (Fig 8), with less than a 10% difference in magnitude over most of the frequency range and somewhat larger differences in narrow ranges in the middle and higher frequencies.

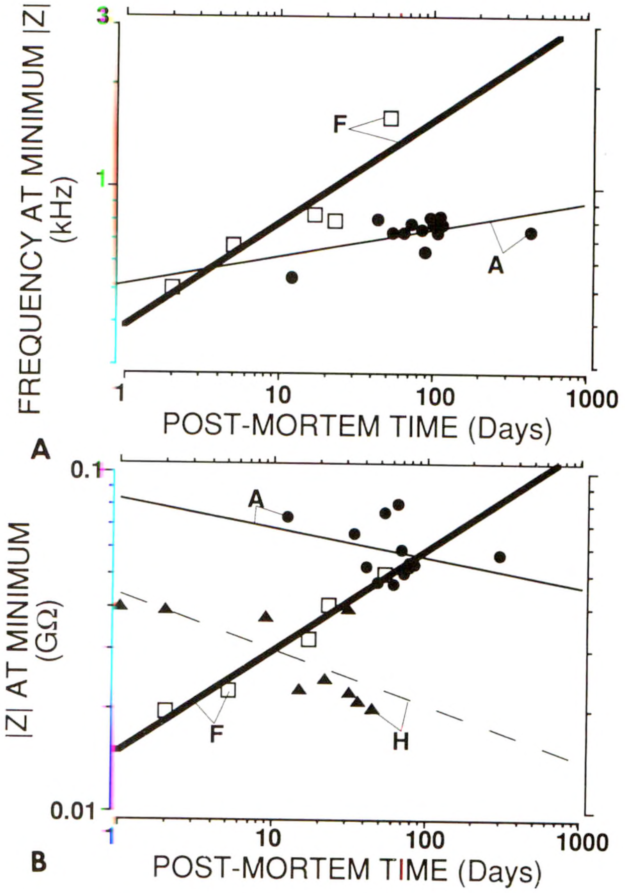

Fig 5. Two plots illustrating changes in input impedance that occurred over time. A) Changes in frequency of impedance minimum (Table 1) in two ears. Change in ear F is statistically significant at 5% level, while change in ear A is not. B) Some changes we observed in magnitude of impedance minimum. Increase in minimum in ear F and decrease in minimum in ear H are significant at 10% level, while decrease in ear A is not significant.

DISCUSSION

Our measurements of middle ear input impedance in 15 ears of temporal bones extracted from human cadavers compare favorably to the normal ranges for living ears defined by Zwislocki and Feldman[10] or by Rabinowitz[11] (Fig 10[10,11]). Between 0.1 and 2 kHz, a majority of the cadaver measurements are within the impedance magnitude ranges observed in normal living ears. Three cadaver ears have impedance magnitudes that are significantly greater than the "normal" magnitude over all of this range (ears C, G, and OC, marked by the thick-

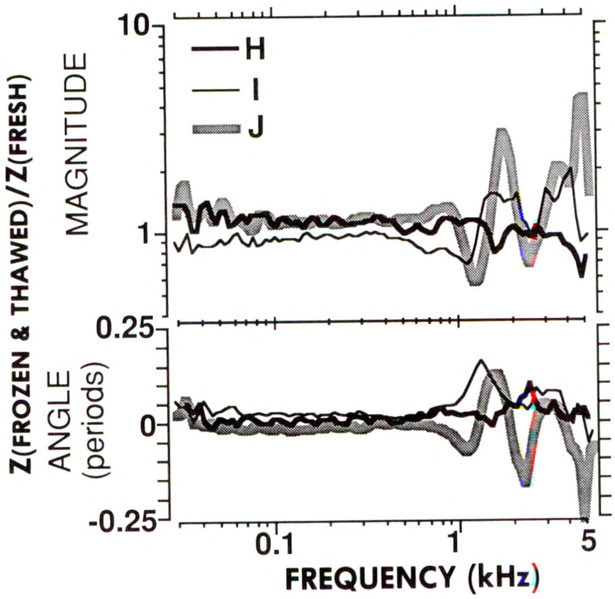

Fig 6. Change in impedance produced by freezing and thawing, assessed by computing ratio of impedance after freezing and thawing to impedance in "fresh" state. Fresh measurements were performed within 24 hours after death.

er black lines) while four other cadaver ears have larger-than-normal impedance magnitudes over some part of this range. One cadaver ear (ear F, marked by the gray line) has an impedance magnitude that is significantly lower than normal over much of the frequency range, while four other cadaver ears have impedance minima that fall somewhat below the normal range. All of the impedance angles from the cadaver ears fit into the normal range between 0.1 and 0.4 kHz, but at higher frequencies, the median angle of cadaver impedances slowly becomes more positive than the median of the normal impedance angles. The result of this divergence is that by 2 kHz most of the cadaver ears have angles that are more positive than those found in the two normative studies.

In the 0.1- to 2-kHz range a majority of the cadaver ears we have investigated exhibit impedances that are indistinguishable from those of normal live ears. Above 2 kHz, the in vitro impedances are significantly different from the impedance of the four young subjects in Rabinowitz's[11] study, but different techniques in different laboratories yield a wide range of high-frequency impedance measurements, some of which are more comparable to the in vitro measurements.[23,24]

There are many possible reasons for the small differences observed between the impedances of the cadaver and living middle ears.

Selection of Subjects. In the in vivo measurements, the definition of a "normal" ear is dependent on the presence of a normal audiogram, and ears with conductive hearing losses are removed from consideration. In our in vitro measurements, audiograms were not available to help restrict the study population; instead, the only criteria for exclusion were either obvious middle ear disease or a nonpeaked tympanogram. Indeed, more selective tympanometric screening (eg, rejecting the three ears with abnormal static impedances: C, G, and OC) would have excluded the three ears with the largest low-frequency impedance magnitudes and would have greatly improved the comparison of Fig 10.[10,11]

Effect of Modified Middle Ear Air Spaces. One of the differences between the prepared temporal

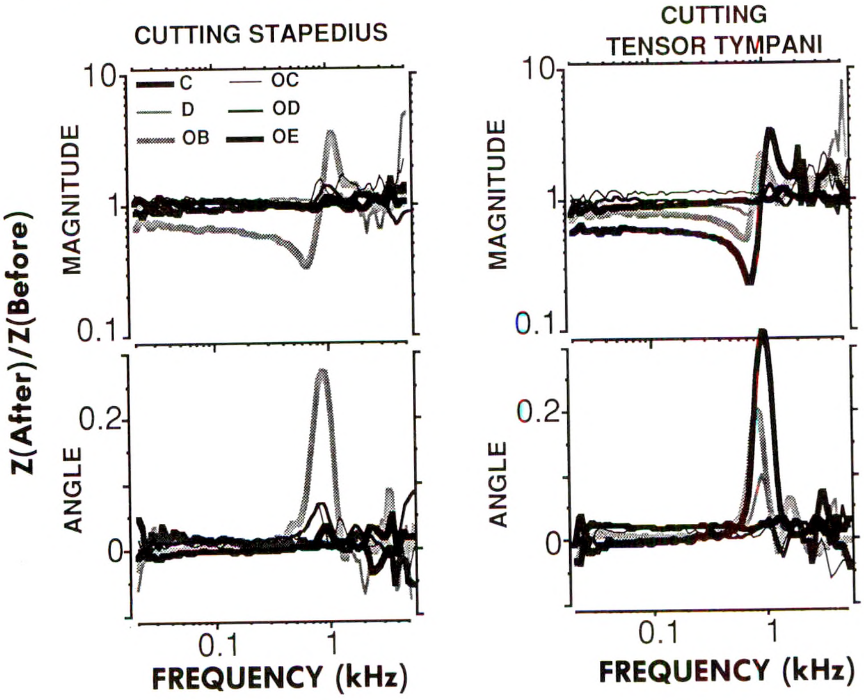

Fig 7. Change in impedance produced by sectioning stapedius and tensor tympani tendons in six ears. "Before" measurements were made after surgical preparations required to expose muscle and just before sectioning muscle.

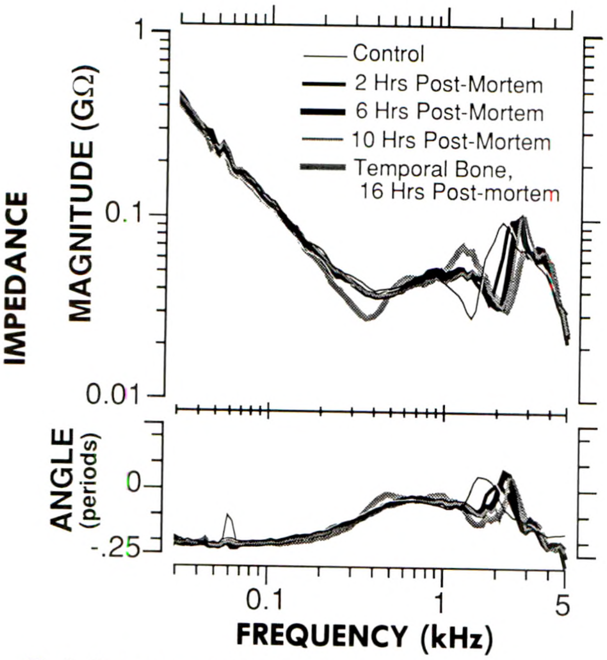

Fig 8. Premortem and postmortem impedances of guinea pig middle ear. Small changes are apparent in some frequency ranges. Largest changes occur immediately after death in 1- to 2-kHz range and after removing temporal bone at 16 hours postmortem.

bones in this study and normal human middle ears is that the mastoid air spaces in the bones have been opened to the atmosphere by the saw used in the extraction procedure. In the normal ear, the middle ear input impedance Z_{ME} results from the sum of impedance due to the air within the middle ear cavity Z_{CAV} and the combined impedance of the tympanic membrane, ossicles, and cochlea Z_{TOC},[25] such that

$$Z_{ME} = Z_{TOC} + Z_{CAV} \qquad (2)$$

Opening the middle ear air spaces essentially reduces Z_{CAV} to zero.

The effect of opening the air spaces on the middle ear impedance depends entirely on the relative magnitude of the impedance of the air within the closed middle ear cavities and the impedance of the rest of the middle ear system. In animals in which the impedance of the air space is large compared to the impedance of the rest of the middle ear (eg, guinea pigs, hamsters, and chinchillas) the middle ear input impedance approximates the impedance of the cavities themselves: $Z_{ME} \approx Z_{CAV}$. Opening the middle ear cavities in these animals results in large decreases in the middle ear impedance.[26-29] In animals in which the impedance of the middle ear air spaces and the tympanic membrane–ossicles and cochlea are nearly of equal magnitude (eg, cat) opening the cavities reduces the middle ear input impedance by a factor of 2.[25,26,30] In humans, the impedance of the middle ear air spaces is at least a factor of 3 smaller than the impedance of the rest of the middle ear ($Z_{CAV} << Z_{TOC}$), and the middle ear input impedance approximates the impedance of the membrane, ossicles, and cochlea: $Z_{ME} \approx Z_{TOC}$.[31] Therefore, opening the air spaces has little effect on the human middle ear input impedance. This disparity between the impedance of the tympanic membrane–ossicles–cochlea and the middle ear air spaces can be directly observed by comparing the impedances measured in our cadaver ears with the impedance of the middle ear air spaces in normal humans. The data of Fig 2 point out that at low frequencies ($f < 400$ Hz) the middle ear input impedance in our temporal bones is primarily compliant and can therefore be described in terms of the volume of air with an equivalent impedance. Rewriting equation 2 in terms of equivalent volumes of the impedance yields

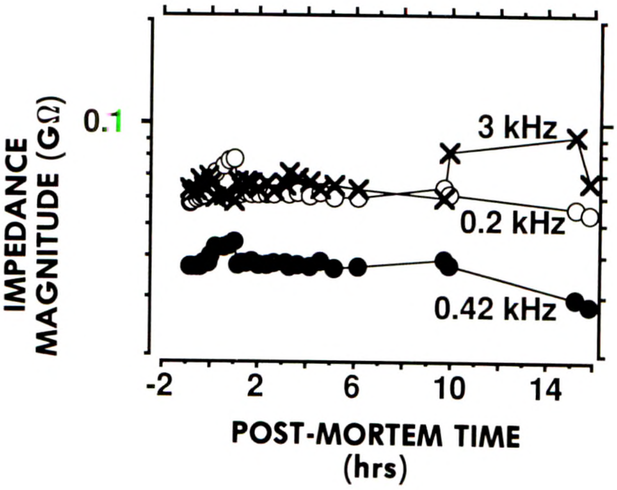

Fig 9. Time course of postmortem changes observed in impedance magnitude of guinea pig ear (same ear as in Fig 8). Last two measurement points at each frequency were gathered after removing temporal bone.

$$\frac{\rho 0c^2}{j2\pi f V_{ME}} = \frac{\rho 0c^2}{j2\pi f}\left(\frac{1}{V_{TOC}} + \frac{1}{V_{AIR}}\right) \qquad (3)$$

where V_{ME} is the equivalent volume of the total input impedance of the middle ear, V_{TOC} is the equivalent volume of the tympanic membrane, ossicles, and cochlear load, and V_{AIR} is the volume of air within the middle ear cavity. The equivalent volumes of the input impedance measured in our 15 ears ranges from 0.2 to 1.1 mL with a median of 0.6, whereas Molvoer et al[32] report that the volume of the middle ear air spaces in normal ears varies between 1.9 and 21 mL with a median of 6. The median values suggest that opening the middle ear air spaces decreases the low-frequency middle ear input impedance by less than 10%, while a worst-case analysis suggests a decrease of no more than 50%. Roberto and Zito[14] noted impedance changes of 10% to 50% when they widely opened the eustachian tubes in temporal bones. At higher frequencies the effect of opening the middle ear air spaces becomes more complicated, but the work of McElveen et al[1] suggests that these effects are also small

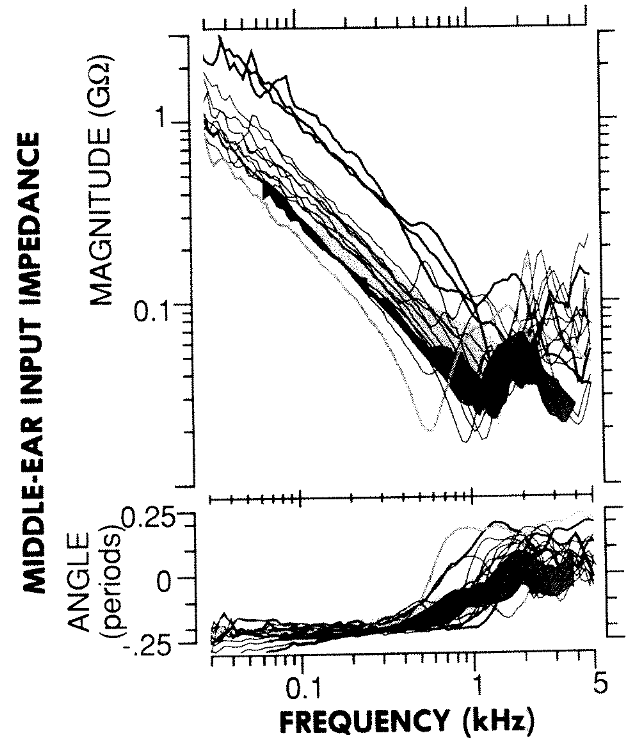

Fig 10. Comparison of in vitro impedance measurements in 15 cadaver middle ears with range of impedance magnitude and angles observed in several in vivo measurements. Areas of lighter shading are 10th to 90th percentile ranges of impedances of 33 subjects with normal hearing,[10] while areas of darker shading are ranges of impedance measurements in four young males with normal hearing.[11] Thicker black lines are impedances measured in three ears (C, G, and OC) with peaked but stiff tympanograms (type AS). Gray line is impedance measured in ear (F) with largest static compliance.

as long as the aditus is kept intact (as has been done in this study).

Age Differences. There is a considerable difference in the median age between the cadaver ears and the ears of normal subjects in the other studies. The median age of the cadaver ears is around 68 years, while the normal subjects of the Zwislocki and Feldman[10] study were of mixed age and the subjects of the Rabinowitz[11] study were all less than 30 years old. The effect of age on the middle ear mechanisms is enigmatic, since various authors suggest a decrease, increase, or no change in the input impedance of the aged middle ear. (See Marshall et al[33] for a review.) The results from the present study that bear on this issue are inconclusive. No correlation is observed between age and the impedance in the 15 cadaver ears; however, the study population is heavily skewed toward ages of >50 years and does not provide an adequate test of age effects.

Freezing and Thawing. Some authors have suggested that freezing and thawing cause changes in the middle ears of temporal bone plugs.[34] However, direct comparisons of impedance in ears before and after freezing indicate that any effects of freezing are small (Fig 6).

Postmortem Changes in Middle Ear Muscles. There has been some concern that postmortem changes in the middle ear muscles may alter the impedance of cadaver middle ears. The measurements reported here (Fig 7) and similar measurements by Gyo et al[3] suggest that these muscles generally have small effects on the mechanics of the middle ears of cadavers.

Rapid Postmortem Changes. Because of the delay between death and extraction of the temporal bones, the in vitro data cannot rule out the presence of rapid postmortem changes in the middle ear. The only evidence on this issue comes from animal studies in which the impedance or motion of the middle ear has been monitored immediately before and after death. The data of Brenkman et al[16] suggest that large alterations in middle ear motion occur in guinea pigs shortly after death. However, some of the postmortem variations that they report are no larger than premortem variations and it is not clear that the static pressure within the guinea pig's middle ear cavity was equalized to ambient pressure. Certainly, the guinea pig results reported here and the results of Khanna and Tonndorf[35] in the cat suggest that the middle ear can remain relatively normal for hours after death.

Slow Postmortem Changes. Some small, slow-acting postmortem changes in the middle ear have been observed in this study. These changes are only apparent in a few ears, and the time constant of the changes that did occur is larger than 100 days. Furthermore, there is no relationship between the features of the first impedance measured in all of the cadaver ears and the time since death. Brenkman et al[16] also suggest that the middle ear function of extracted human temporal bones is stable over periods of several days.

Effect of Cochlear Load. The middle ear input impedance is known to be sensitive to the cochlear load, since destruction of the cochlear partition or draining of the inner ear fluids will cause large changes in middle ear motion and impedance[4,25,30] at low and moderate frequencies. Because of this dependence, the cochlea must remain fluid-filled in order for the middle ear to function normally. There are also more subtle effects of the cochlea on the middle ear mechanics. At higher frequencies (>10 kHz) the impedance can be altered by more restricted damage to the inner ear sensory mechanism.[36] Furthermore, alterations in cochlear efferent activity[37] may cause small but noticeable changes in the middle ear input impedance of cats. Although the subtle changes caused by either efferent activity or local damage to the inner ear seem to occur only at frequencies above our measurements in cadaver ears, the gross broadband changes in middle ear function that are produced by draining the scalae are a concern. Indeed, the most prominent long-term changes we have observed are similar to what would be expected if the inner ear fluids were slowly draining.

Effect of Ear Canal. As has been pointed out by Zwislocki and Feldman,[10] Møller,[20,25] and Rabinowitz,[11] the actual measurements of impedance made in ear canals include the effect of the ear canal air space between the acoustic source and the tympanic membrane. Corrections for this effect are more complicated for larger ear canal air spaces. In our preparation we placed the acoustic source within 1 mm of the tympanic membrane and greatly reduced the size of the ear canal space. The small size of the remaining ear canal and the proximity of the source to the tympanic membrane allowed us to accurately approximate this space with a simple acoustic compliance. More complicated correction procedures (eg, the transmission line corrections of Møller[20] and Rabinowitz[11]) yielded identical results.

Effects of Temporal Bone Removal. It is unlikely that simple removal of the temporal bone can cause large changes in the middle ear, since in the one guinea pig ear in which impedance was measured before and after removal of the temporal bone (Fig 8) the change in the impedance was minimal.

CONCLUSIONS

The in vitro input impedances of a large fraction of cadaver middle ears are indistinguishable from the available in vivo measurements in normal ears; however, these results are contingent on keeping the extracted middle ears moist and controlling the middle ear air pressure. Freezing and thawing have no great effect on the in vitro impedance; nor does sectioning the tendons of the middle ear muscles. These results suggest that the middle ears of extracted human temporal bones can be useful models for studies of middle ear function and reconstruction. Indeed, this preparation is already being used to investigate complexities of ossicular motion[4,5,38,39] in the human ear and test the efficacy of various reconstructive surgical procedures.[6] A major problem in these efforts is selecting those cadaver ears with normal middle ear function. Our results also suggest that tympanometry may be useful, since all of our cadaver ears with normal input impedance had normal tympanograms.

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Ann Otol Rhinol Laryngol 99:1990

IMAGING CASE STUDY OF THE MONTH

MEDIASTINAL BRONCHOGENIC CYST

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CHARLES M. MYER III, MD GLENN O. BRATCHER, MD
CINCINNATI, OHIO

Bronchogenic cysts are congenital foregut duplication anomalies that may be discovered incidentally on chest radiographs or when they produce symptoms by compression of the thoracic trachea or other mediastinal structures. In the past, a chest radiograph and barium esophagogram were the standard radiographic modalities used to evaluate this entity. More recently, computed tomography has emerged as the radiographic study of choice. We report a case of a symptomatic mediastinal bronchogenic cyst diagnosed by magnetic resonance imaging.

CASE REPORT

A 7-month-old boy, the product of a normal gestation and delivery, developed a transient episode of stridor accompanying an upper respiratory tract infection 2 months prior to presentation. Symptoms were self-limited and quickly resolved. He was then asymptomatic until presenting to the emergency room with an upper respiratory tract infection accompanied by wheezing and dyspnea. His symptoms responded immediately to bronchodilator inhalants. The neck radiographs (Fig 1) obtained at that time demonstrated marked narrowing of the thoracic trachea. Microlaryngoscopy and bronchoscopy revealed a normal larynx but significant anterior-posterior narrowing from the subglottic region extending down to the carina (Fig 2). Magnetic resonance imaging demonstrated a well-defined, 4 x 3.5 x 2.5-cm cystic mass in the posterior mediastinum, between the trachea and esophagus (Fig 3). The mass was excised via a thoracotomy, with resolution of symptoms. Endoscopy performed immediately postoperatively revealed an 80% reexpansion of the airway. Pathologic examination confirmed a bronchogenic cyst lined with ciliated columnar epithelium, smooth muscle cells, and submucous glands.

DISCUSSION

Bronchogenic cysts are congenital anomalies that occur during the 26th to 40th days of gestation from abnormal budding of the ventral foregut, which later differentiates into the tracheobronchial tree.[1] Related anomalies include sequestration malforma-

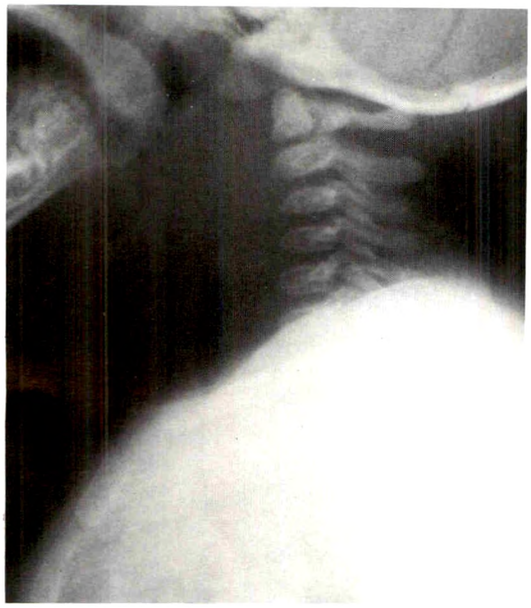

Fig 1. Lateral neck radiograph revealing marked anterior-posterior narrowing of thoracic trachea.

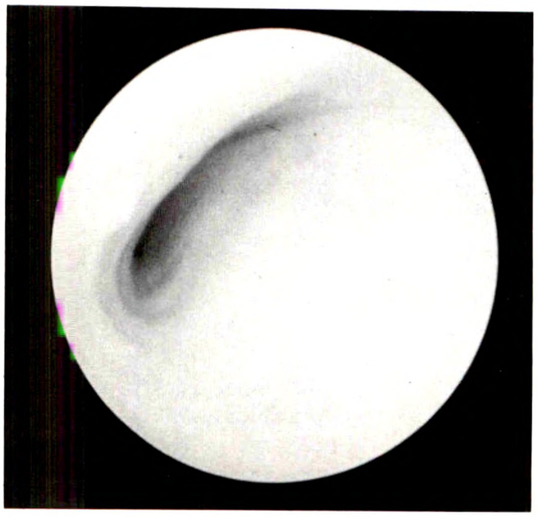

Fig 2. Endoscopic view of midthoracic trachea demonstrating significant posterior tracheal compression.

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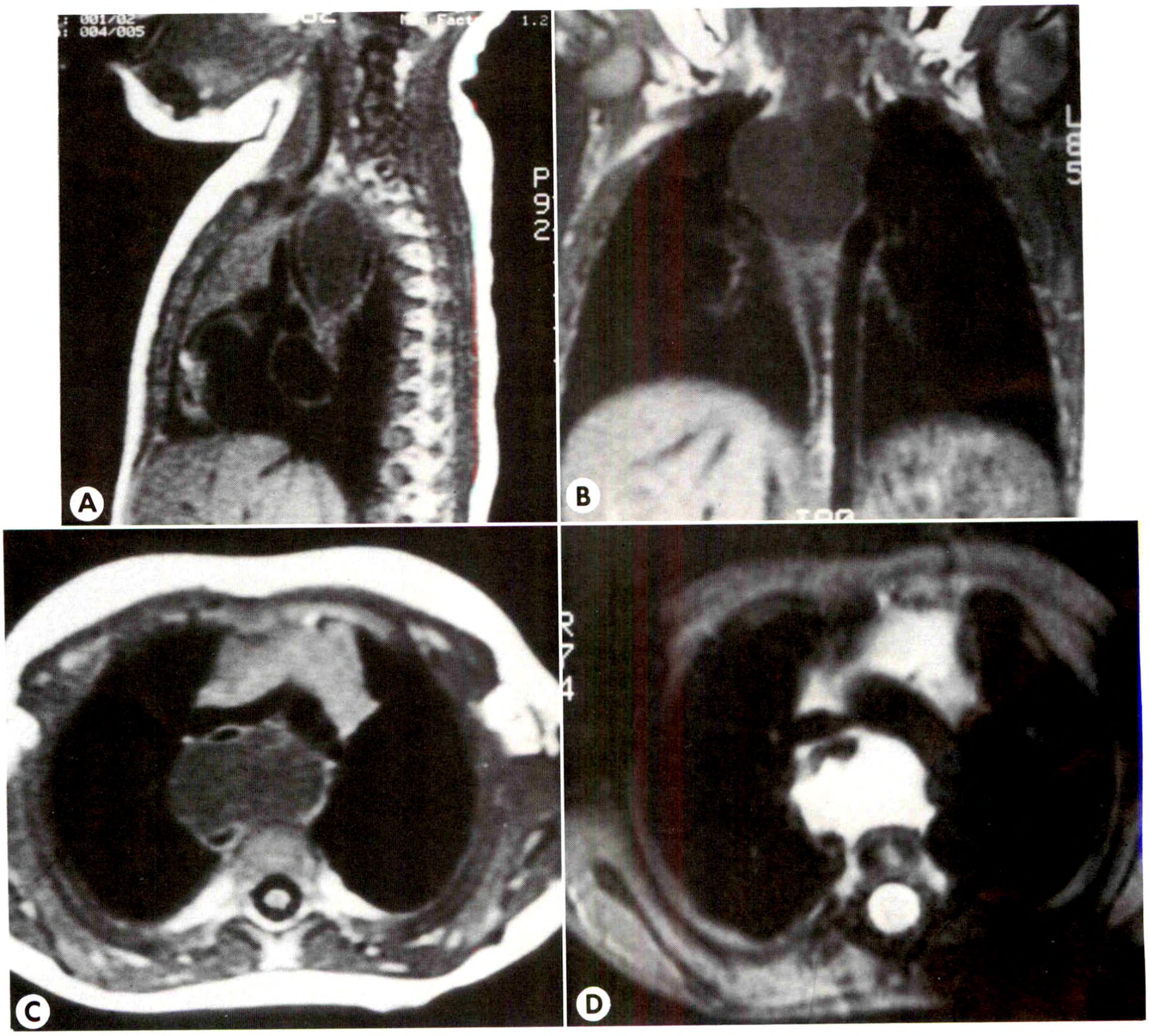

Fig 3. Large, cystic mass located in posterior mediastinum interposed between trachea and esophagus, demonstrated on A) sagittal, B) coronal, and C) axial T1-weighted magnetic resonance imaging sections (TR = 429, TE = 20). D) T2-weighted scan demonstrates cystic nature of mass (TR = 429, TE = 25).

tions and tracheal lobes.[2] Bronchogenic cysts usually occur in the posterior mediastinum, near the carina. However, they may arise in extrathoracic locations such as the lower neck and abdomen.[3] In addition, these lesions may be found intralobar (ie, within the pulmonary parenchyma) or, more commonly, extralobar. Bronchogenic cysts arising within the trachea have also been reported.[4] There is usually an attachment to the major airways or esophagus by dense fibrous tissue, but only rarely is a patent communication demonstrated. Approximately 75% of these lesions become infected at some time; a patent communication to the airway is more common then.[1] Foregut cysts account for approximately 14% of all thoracic masses in children[5] and approximately 20% of primary mediastinal masses in adults and children.[6]

Bronchogenic cysts may be an incidental radiographic finding or may produce symptoms by compressing mediastinal structures. Wheezing, dyspnea, stridor, and recurrent pneumonias all have been reported, as well as acute airway obstruction caused by an intratracheal cyst.[4] Cardiovascular manifestations have also been reported, including left pulmonary artery compression, pulmonary stenotic murmurs, superior vena cava syndrome, and cardiac arrhythmias.[3,7-11]

The treatment of choice for bronchogenic cysts is thoracotomy and complete excision of the lesion, particularly in younger patients, because of the potential risk of recurrent infections. Transtracheal needle aspiration of these lesions has been described for acute decompression or definitive treatment.[12]

Radiographically, bronchogenic cysts are typically homogeneous, of fluid density, and ovoid or spherical in shape, and they have sharply defined margins.[13] Computed tomography has proven to be superior to plain radiography and barium esophagography in the diagnosis of bronchogenic cysts. The relationship to surrounding structures is better demonstrated, the cystic nature of the lesions is established, and cryptic foregut cysts are better identified. During computed tomography, bronchogenic cysts do not enhance when contrast medium is administered, but contrast studies may help delineate the lesion by enhancing surrounding mediastinal structures.

Magnetic resonance imaging is the latest radiographic modality in our diagnostic armamentarium. Better resolution and detailed sagittal imaging are valuable in the diagnosis and preoperative assessment of bronchogenic cysts, as is demonstrated in this case.

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PATHOLOGY CONSULTATION

SEBACEOUS LESIONS OF SALIVARY GLANDS AND ORAL CAVITY

JOHN G. BATSAKIS, MD ADEL K. EL-NAGGAR, MD, PHD

HOUSTON, TEXAS

Sebaceous differentiation in the oral mucosa and major salivary duct epithelium is an expected normal finding in humans. These usually asymptomatic and incidental collections of sebaceous cells can also be found in intimate or close relationship with definable classes of salivary gland neoplasms, or as sebaceous neoplasms of salivary glands. The neoplasms are uncommon and are classified as sebaceous lymphadenoma, sebaceous adenoma, and sebaceous carcinoma. The two adenomas have a low recurrence potential; the carcinomas have a biologic behavior like that of ocular sebaceous carcinomas.

Sebaceous glands are prominent adnexal components of skin, normally found either closely associated with hair follicles (90%) to form the pilosebaceous apparatus, or independently in the skin. The distribution of the glands is uneven, with the face and scalp the areas with the greatest density of glands. Normal glands vary in size from 0.2 to 2.0 mm in diameter, with the largest in the skin of the nose and concha of the ear.[1] The glands are alveolar-holocrine, with their lipidic secretions formed by disruption of individual cells. Sebum, thus formed, is discharged via a short duct.

Extracutaneous, extraocular sebaceous glands in the head and neck are principally found in the oral cavity and in the major salivary glands. Sebaceous glands on the lips or buccal mucosa (Fordyce's granules) of humans or higher apes are so common as to be considered the norm rather than exceptional.[1-3] Nearly 80% of adults will show the characteristic yellow-white, single or grouped, pinhead-size granules at these two sites of predilection. Less often they can be found on the retromolar region of the palate, the tongue, frenum, alveolar gingivae, and anterior pillars of the tonsils. The lower lip, especially its central part, is usually devoid of sebaceous glands. It is rare to find sebaceous glands in the oral cavities of subjects younger than 3 years.

SEBACEOUS GLAND DIFFERENTIATION IN MAJOR SALIVARY GLANDS

Condition	*Estimated Frequency/No.*
Expected normal constituent	30% to 40% of all adult parotid glands. Can be found throughout life, including neonatal glands; 5% of adult submandibular glands
Histologic accompaniment of salivary gland tumors (within or near)	20%; seen most often in Warthin's tumors, low-grade mucoepidermoid carcinomas, and monomorphic and pleomorphic adenomas
Classifiable sebaceous neoplasms	
Sebaceous lymphadenoma	31 in parotid gland by 1983[5]
Sebaceous carcinoma	22 in parotid gland by 1989[7]
Sebaceous adenoma	13; 11 in parotid and 2 in submandibular glands by 1983[5]

Information from Linhartova,[3] Gnepp,[5] Batsakis et al,[6] and Takata et al.[7]

Other than an unusual prominence in some patients, intraoral sebaceous glands usually are asymptomatic. Tumoral sebaceous lesions are most often hyperplastic-hypertrophic rather than neoplastic.[4] Carcinomas are exceedingly rare.

Typical sebaceous cells and glands, even manifesting a holocrine secretion, are also found in normal major salivary glands, most often the parotid glands (see Table[3,5-7]). In these glands, their presence is not attributable to an ectopia, but represents yet another potential of differentiation by the salivary duct unit. In the intercalated and striated ducts, the sebaceous elements usually form only cell clusters. Larger accumulations with a more glandlike and diverticular aspect are seen in the inter-

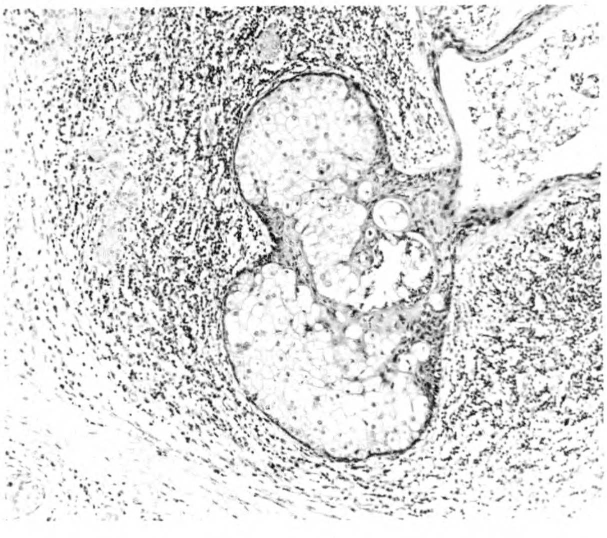

Fig 1. Sebaceous gland differentiation extending from interlobular duct in chronic sialadenitis of submandibular gland (H & E, original x65).

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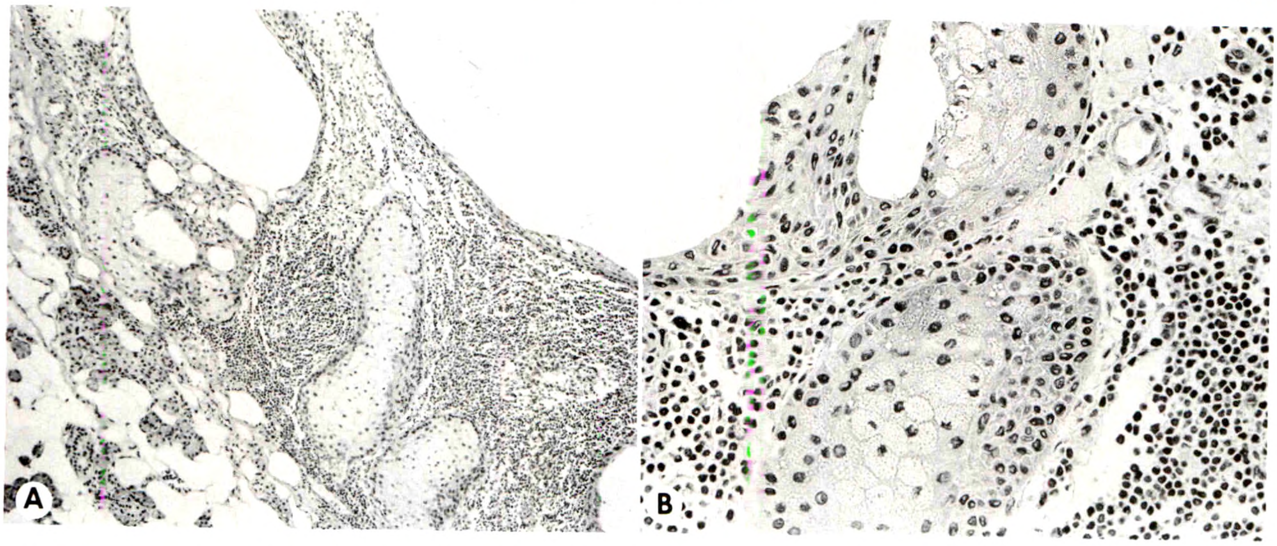

Fig 2. Sebaceous lymphadenoma of parotid gland. A) Arising within intraparotid lymph node (H & E, original x50). B) H & E, original x160.

lobular ducts. In the parotid glands the sebaceous elements may be found throughout the human life span, including the neonate. Another nonneoplastic state of the major salivary glands in which sebaceous glands are found is chronic sialadenitis, in which interlobular and intralobular ducts manifest this differentiation, perhaps as a form of metaplasia in response to the chronic inflammation (Fig 1).

Since sebaceous differentiation of salivary ducts is an expected phenomenon in normal and inflamed salivary tissues, its presence in salivary neoplasms should also be anticipated. The Table[3,5-7] indicates it takes two forms: 1) as a part of otherwise classifiable benign or malignant neoplasms, and 2) as the sole or preponderant proliferating component.[6,8,9] In the former, the sebaceous differentiation is well developed, may be incidental to the primary neoplasm, and does not appear to modify the biologic course of the neoplasm. As for sebaceous neoplasms, there is a fine line of distinction in many of the benign lesions between a hamartomatous hyperplasia and hypertrophy and true neoplastic growth. Most are called adenomas by convention.

The sebaceous lymphadenoma is so named because its origin, like that of Warthin's tumor, is from enclaved salivary tissues in parotid or periparotid lymph nodes.[6,10,11] It is classified as a form of monomorphic adenoma, yet requires both sebaceous and lymphoid components for histopathologic diagnosis. The sebaceous lymphadenoma is histologically characterized by islands of sebaceous differentiating cells and metaplastic salivary ducts diffusely distributed in lymphoid tissue (Fig 2). The islands may be solid, but more often are cystic (microcysts and macrocysts), with secretory products within the cysts. A localized foreign body reaction is provoked after escape of the cystic contents into the lymphoid tissue.

Sebaceous adenomas are typically circumscribed and devoid of an integral lymphoid component. They may be solid or cystic (Fig 3).

"Pure" sebaceous carcinomas of salivary glands are rare, are almost exclusively parotid in origin, and must always be clinically and pathologically distinguished from a secondary involvement by a contiguous or more remote sebaceous carcinoma of the skin of the head and neck.[6,7,9] Sebaceous lymphadenocarcinomas are medical curiosities.[8]

The carcinomas, like their counterparts in the skin, vary in their degree of cytodifferentiation (Fig 4). For an unequivocal diagnosis, there should be areas of recognizable sebaceous cells, with transitions to less-differentiated carcinoma. Intracellular mucin may be found, and is not unexpected because of the carcinomas' origin from ductal epithelium. The carcinomas' high lipid content is helpful in dif-

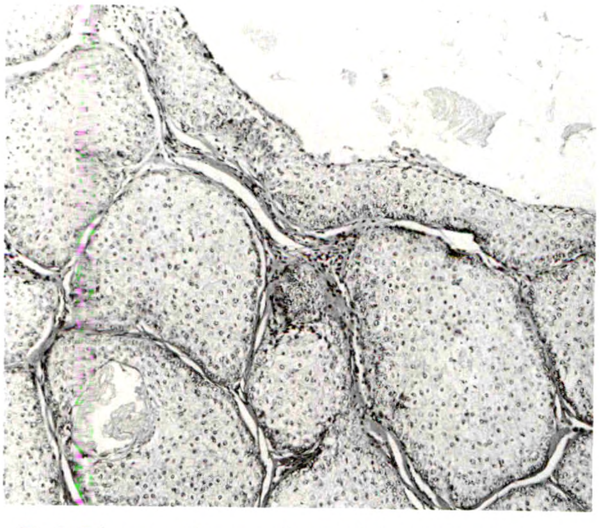

Fig 3. Sebaceous adenoma of parotid gland (H & E, original x65). Adenoma was partly cystic and partly solid and composed only of sebaceous cells.

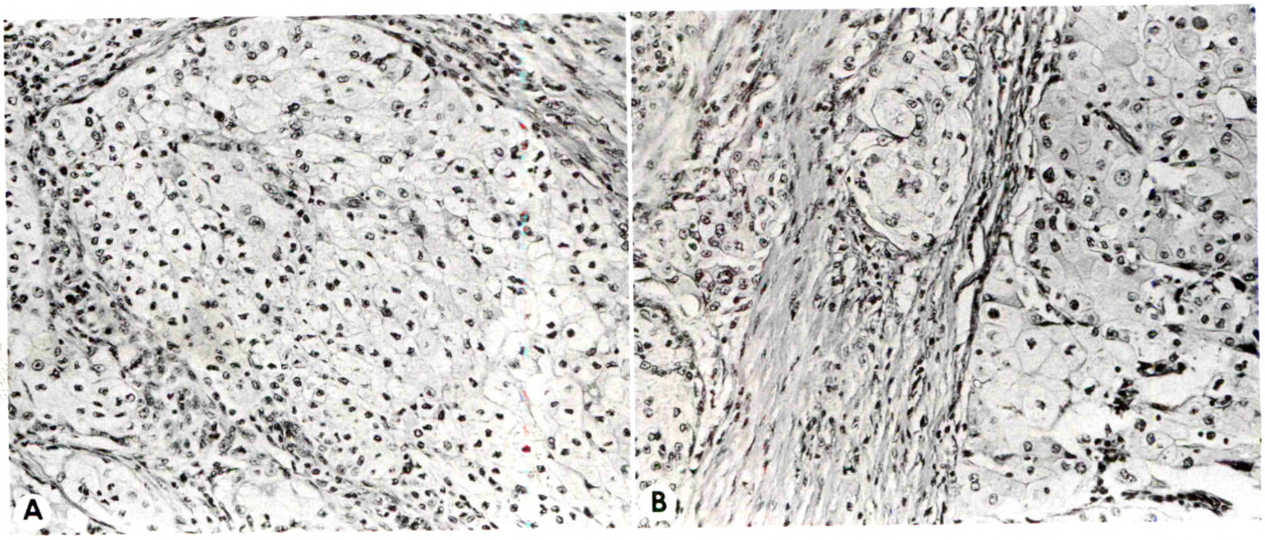

Fig 4. Primary sebaceous cell carcinoma of parotid gland. A) Note retention of sebaceous characteristics by carcinoma (H & E, original x160). B) Groups of malignant sebaceous cells are intersected by fibrous bands (H & E, original x180).

ferential diagnosis, but may be lost during tissue processing for microscopic examination. The lipid further lacks complete diagnostic specificity. Some of the carcinomas may be deceptively circumscribed, but areas of invasion, necrosis, intratumoral fibrosis, and invasion of nerves appropriately place the lesions into the carcinoma class.

Sebaceous carcinomas of the parotid gland exhibit a bimodal age distribution with peak incidences in the third and sixth to ninth decades of life.[7,9] They have a 62% 5-year survival, sharing this aggressiveness with sebaceous carcinomas arising in the eyelids, caruncle, and orbit, unlike other extraocular sebaceous carcinomas.[7,12]

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LETTERS TO THE EDITOR

To the Editor:

T. N. Kaiser, D. G. Sessions, and J. E. Harvey present a series of 373 patients treated with hemilaryngectomy (271) or irradiation (102) at Washington University, St Louis, Mo, between 1972 and 1987 for T1N0 squamous cell carcinoma of the glottic larynx (Natural history of treated T1N0 squamous carcinoma of the glottis, *Ann Otol Rhinol Laryngol* 1989;98:217-9). These patients were culled from 489 patients with squamous cell carcinoma of a single vocal cord; 54 (11%) were lost to follow-up and excluded from further study. As the data were published in 1989, minimum follow-up was presumably less than 2 years, and maximum follow-up was approximately 16 years. The overall local recurrence rate was 16.6% for hemilaryngectomy and 34.3% for radiation therapy. Thirty percent of local recurrences following hemilaryngectomy and 20% of local failures after irradiation were observed more than 5 years after completion of treatment. There are several points with which we take issue.

1. The authors incorrectly state that the final "cure rate" is usually defined as nonrecurrence prior to 5 years after initial therapy. They imply that their method of local control analysis differs in that local failures occurring after 5 years are scored as such, giving a more realistic approximation of the overall local recurrence rate following treatment. In most published data (at least in the irradiation-alone series), local control is calculated using the same method employed by Kaiser et al.

2. The local control rate for T1 lesions treated with irradiation alone (66%) in this series is substantially lower than that reported by most institutions. Local control with irradiation alone in 184 patients with T1 glottic carcinoma treated at the University of Florida, Gainesville, was 172 of 184 patients (93%).[1] In the subset of T1 vocal cord cancer limited to one cord, local control with irradiation was 141 of 151 patients (93%). The ultimate local control rate, including patients surgically salvaged for local recurrence, was 179 of 184 patients (97%), and the rate of local control with larynx preservation was 174 of 184 patients (95%). Follow-up ranged from 2 to 22 years; 82% were observed for ≥5 years, 41% for ≥10 years, and 22% for ≥15 years. Only 2 patients (<1%) were lost to follow-up, at 2 and 6.5 years, respectively. Amornmarn et al[2] reported local control in 79 of 86 patients (92%) treated for T1 vocal cord cancer with irradiation alone at the University of Maryland, Baltimore; follow-up ranged from 5 to 23 years. Kelly et al[3] reported local control in 90 of 95 patients (95%) treated with irradiation for T1 glottic carcinoma at the University of Virginia, Charlottesville, with 3 to 16 years of follow-up. Four of five local recurrences were successfully salvaged with a hemilaryngectomy, so that 94 of 95 (99%) had local control with voice preservation. Local control in these three series was calculated in the same manner as that used by Kaiser et al, and the follow-up in these series was as long as or longer than that reported in Kaiser's series. Mittal et al[4] reported a series of 177 patients treated with irradiation alone at Washington University between 1952 and 1978 for T1N0 vocal cord carcinoma with follow-up ranging from 2 to 15 years. They noted local control in 84% with irradiation alone and a 90% local control rate with voice preservation, including patients salvaged by hemilaryngectomy for local failure. Local control was calculated in the same manner as that used by Kaiser et al, yet the local control rates for irradiation at the same institution are quite different — 84% as opposed to 66%.

3. Kaiser et al noted that of those patients who developed local recurrence, 30% of the recurrences occurring after hemilaryngectomy and 20% occurring after irradiation were observed >5 years after treatment. This is in contrast to data reported in the literature. Forty-one of 304 patients treated with irradiation alone for T1 or T2 vocal cord carcinoma at our institution developed recurrent disease: 83% within 2 years of treatment, 93% within 3 years of treatment, and 98% within 5 years of treatment. The only patient who developed recurrence after 5 years did so at 6 years 2 months following irradiation. This difference is all the more striking when one considers that the follow-up in our series was substantially longer than that reported by Kaiser et al. Patients treated for head and neck cancer in our institution are examined periodically in our clinic indefinitely; follow-up is not relegated to a tumor registry after 5 years. In our series, any vocal cord recurrence was scored as a local recurrence, even if it was located in the opposite, previously uninvolved cord.

4. The authors state that the cost of irradiation is two thirds to three fourths the cost of a hemilaryngectomy. We are unable to compare these costs at our institution because hemilaryngectomy is not used initially to manage previously untreated early vocal cord cancer. However, Mittal et al[5] reported that hemilaryngectomy cost more than twice as much as a course of irradiation for T1N0 vocal cord cancer managed at the authors' institution, Washington University, in 1980-1981.

Irradiation and hemilaryngectomy offer similar cure rates for T1 to T2 vocal cord cancer; irradiation is associated with better voice quality following treatment.

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To the Editor:

Thank you for the opportunity to respond to the letter of Mendenhall et al. Our study compared certain outcome results of patients with T1N0 epidermoid cancer of the true vocal cord treated initially with either hemilaryngectomy or radiation therapy. All of these patients had cancer confined to one membranous vocal cord. None had involvement of the anterior commissure or the vocal process and none had subglottic extension of their tumor. All patients were eligible for 3-year follow-up.

The initial issue brought up is one of the method of end results reporting. We agree that this issue needs addressing. Despite the fact that we work very closely with our colleagues in radiation therapy, we use different methods of reporting the outcome of our treatments. Head and neck surgeons report results as disease-free interval (DFI). For instance, in this paper we reported DFI as time from initial treatment until failure at intervals of less than 3 years, 3 to 5 years, and greater than 5 years. In general, surgeons also discuss the phenomenon of survival (being alive) as either determinate, actuarial, or absolute (all patients in the study). On the other hand, the radiation therapy literature discusses local control, regional control, distant control, and overall control, as well as various forms of survival. Obviously, we need to agree to standardize our form of end results reporting.

It is always interesting when the figures in a study do not come out as expected. That does not always mean that either the study or the figures are automatically wrong. We are aware that our local recurrence data for initial treatment of these patients by radiation therapy differ from those found in the literature, including reports from our own radiation therapy department. DeSanto and Lillie[1] and DeSanto and Pearson[2] have also reported higher rates of recurrence of stage I carcinoma of the larynx treated primarily by radiation therapy than those noted by Mendenhall et al.

The patients in our study were initially evaluated in our department and were referred by us for radiation therapy. Ninety-five patients were treated here at Washington University and seven patients were treated elsewhere. Of the seven patients treated elsewhere, six had recurrent cancer. A valid question brought up by our data is, what is it about the patients that we referred for radiation therapy that caused them to have an increased local recurrence rate in comparison to other patients treated by radiation therapy?

Mendenhall et al bring up another linguistic issue in questioning the distinction between a recurrence and a second primary. We have defined a cancer that arises from the original primary site as a recurrence regardless of the time interval. We have defined a cancer arising from a separate site (as on the opposite, previously clean vocal cord) as a second primary. It is abundantly clear that we need to agree on standardizing outcome reporting.

The protocol for follow-up of patients in our department has been published recently.[3] Follow-up examination, diagnosis, and treatment remain the responsibility of the treating surgeon. The tumor registry is an adjunct allowing improved follow-up and more rigorous end results reporting, as well as providing data for evaluating treatment regimens.

The paper compared total treatment costs (including the costs of secondary therapy) of the two patient populations. The total so determined showed that the costs were similar, and this was so because of the difference in the costs of secondary treatment.

To our knowledge there has never been a prospective study of the treatment of early vocal cord cancer.[4] This is because physicians and researchers are so absolutely certain about the best, the right, and the only way to treat these patients. We suggest that these presuppositions may not be entirely correct and that as we continue to study subsets of T1 cancers of the vocal cord this may become more clear.

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To the Editor:

In their introductory comments in a Letter to the Editor,[1] Furman et al went beyond the scientific merits of the paper under question.[2] For this reason I feel it necessary to respond. These authors did provide me with a copy of the manuscript prior to its submission for consideration for publication, and we did have at least two conversations regarding the paper, after which some minor revisions were made. Furman et al were unwilling to make any further changes, presumably because this would have changed the content of the paper from that of oral presentation. When I was asked if they could acknowledge my participation in the review of the paper, I declined because I felt the statistical design was flawed and the conclusions highly questionable.

I am further puzzled by the two separate publications of this material about 2 months apart.[2,3] The papers, while having slightly different titles, are virtually the same. There was no reference to the prior publication in the *Annals*. [*This is commonly done. Original journal contributions often appear elsewhere as book chapters. — ED.*] With regard to the scientific content of the paper, I stand by my previous comments,[4] the subsequent response of the authors notwithstanding.

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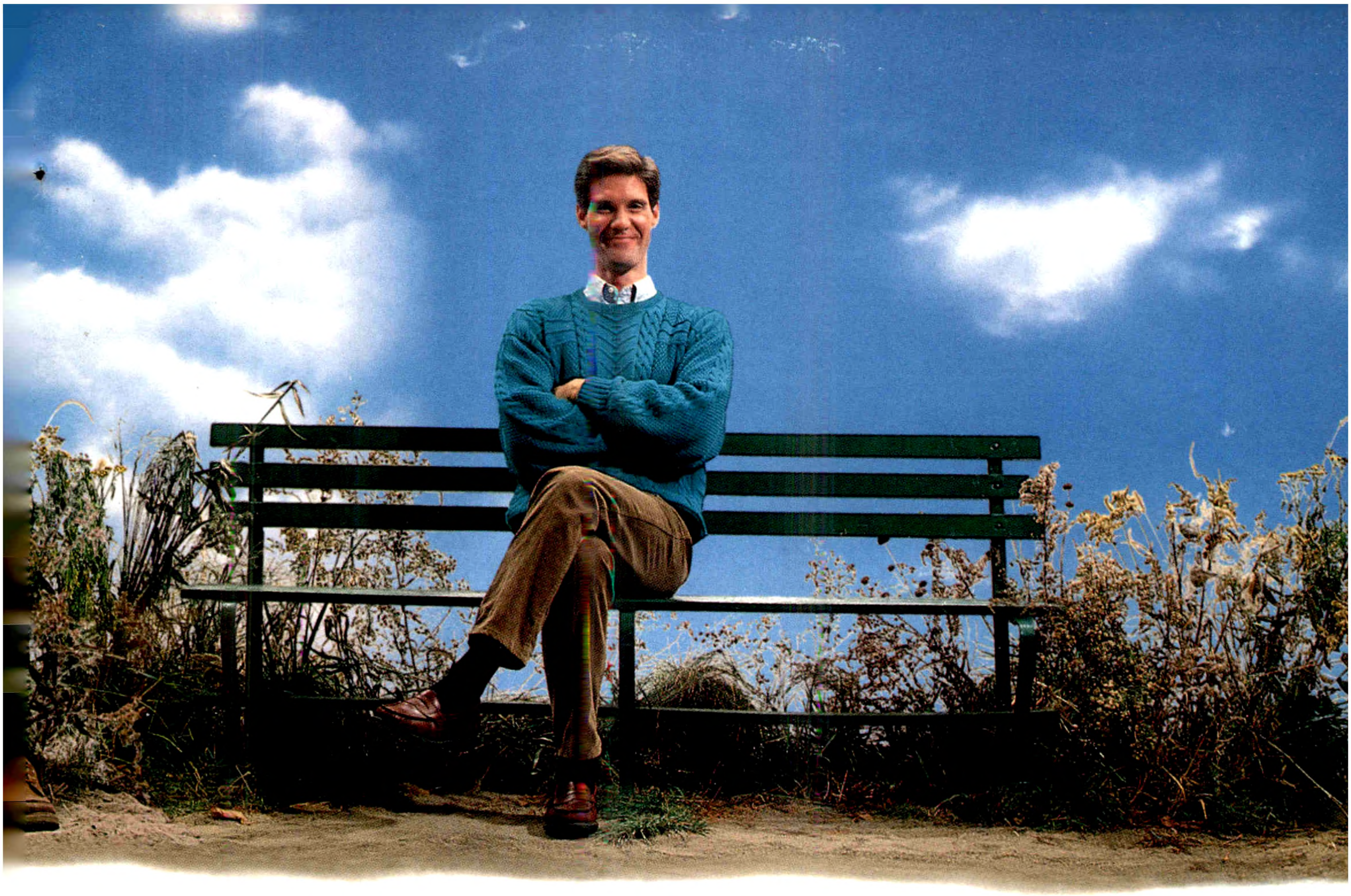

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The following is a brief summary only. Before prescribing, see complete prescribing information in Beconase® Inhalation Aerosol and Beconase AQ® Nasal Spray product labeling.

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of either preparation contraindicates its use.

WARNINGS: The replacement of a systemic corticosteroid with Beconase® Inhalation Aerosol or Beconase AQ® Nasal Spray can be accompanied by signs of adrenal insufficiency.

Careful attention must be given when patients previously treated for prolonged periods with systemic corticosteroids are transferred to Beconase Inhalation Aerosol or Beconase AQ Nasal Spray. This is particularly important in those patients who have associated asthma or other clinical conditions where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that the combined administration of alternate-day prednisone systemic treatment and orally inhaled beclomethasone increases the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, Beconase Inhalation Aerosol and Beconase AQ Nasal Spray treatment should be used with caution in patients already on alternate-day prednisone regimens for any disease.

If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, Beconase Inhalation Aerosol and Beconase AQ Nasal Spray should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy.

PRECAUTIONS: General: During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, eg, joint and/or muscular pain, lassitude, and depression.

Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone.

Extremely rare instances of wheezing, nasal septum perforation, and increased intraocular pressure have been reported following the intranasal application of aerosolized corticosteroids. Although these have not been observed in clinical trials with Beconase AQ® Nasal Spray, vigilance should be maintained.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuation of treatment with Beconase® Inhalation Aerosol or Beconase AQ Nasal Spray.

If persistent nasopharyngeal irritation occurs, it may be an indication for stopping Beconase AQ Nasal Spray.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of Beconase Inhalation Aerosol or Beconase AQ Nasal Spray may suppress HPA function.

Beconase Inhalation Aerosol and Beconase AQ Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; untreated fungal, bacterial, or systemic viral infections; or ocular herpes simplex.

For either preparation to be effective in the treatment of nasal polyps, the aerosol or spray must be able to enter the nose. Therefore, treatment of nasal polyps with these preparations should be considered adjunctive therapy to surgical removal and/or the use of other medications that will permit effective penetration of these preparations into the nose. Nasal polyps may recur after any form of treatment.

As with any long-term treatment, patients using Beconase Inhalation Aerosol or Beconase AQ Nasal Spray over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses of Beconase Inhalation Aerosol and Beconase AQ Nasal Spray should be avoided.

Information for Patients: Patients being treated with Beconase Inhalation Aerosol or Beconase AQ Nasal Spray should receive the following information and instructions. This information is intended to aid in the safe and effective use of medication. It is not a disclosure of all possible adverse or intended effects. Patients should use these preparations at regular intervals since their effectiveness depends on their regular use. The patient should take the medication as directed. It is not acutely effective, and the prescribed dosage should not be increased. Instead, nasal vasoconstrictors or oral antihistamines may be needed until the effects of Beconase Inhalation Aerosol or Beconase AQ® (beclomethasone dipropionate, monohydrate) Nasal Spray are fully manifested. One to two weeks may pass before full relief is obtained. The patient should contact the doctor if symptoms do not improve, or if the condition worsens, or if sneezing or nasal irritation occurs. For the proper use of either unit and to attain maximum improvement, the patient should read and follow carefully the patient's instructions section of the package insert.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of rats for a total of 95 weeks, 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have not been performed.

Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrous cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route.

Pregnancy: *Teratogenic Effects: Pregnancy Category C:* Like other corticoids, parenteral (subcutaneous) beclomethasone dipropionate has been shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately ten times the human dose. In these studies, beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at ten times the human dose or orally at 1,000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Beconase (beclomethasone dipropionate, USP) Inhalation Aerosol or Beconase AQ Nasal Spray is administered to nursing women.

Pediatric Use: Safety and effectiveness in children below 6 years of age have not been established.

ADVERSE REACTIONS: In general, side effects in clinical studies with both preparations have been primarily associated with irritation of the nasal mucous membranes.

Extremely rare instances of wheezing, nasal septum perforation, and increased intraocular pressure have been reported following the intranasal administration of aerosolized corticosteroids (see PRECAUTIONS).

Rare cases of immediate and delayed hypersensitivity reactions, including urticaria, angioedema, rash, and bronchospasm, have been reported following the oral and intranasal inhalation and administration of beclomethasone.

Beconase® Inhalation Aerosol: Adverse reactions reported in controlled clinical trials and long-term open studies are described below. Sensations of irritation and burning in the nose (11 per 100 patients) following the use of Beconase Inhalation Aerosol have been reported. Also, occasional sneezing attacks (10 per 100 adult patients) have occurred immediately following the use of the intranasal inhaler. This symptom may be more common in children. Rhinorrhea may occur occasionally (1 per 100 patients).

Localized infections of the nose and pharynx with *C albicans* have occurred rarely (see PRECAUTIONS).

Transient episodes of epistaxis have been reported in 2 per 100 patients. Ulceration of the nasal mucosa has been reported rarely.

Systemic corticosteroid side effects were not reported during controlled clinical trials. If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, ie, Cushing's syndrome, could occur.

Beconase AQ® Nasal Spray: Adverse reactions reported in controlled clinical trials and open studies are described below.

Mild nasopharyngeal irritation has been reported in up to 24% of patients treated, including occasional sneezing attacks (about 4%) occurring immediately following use of the spray. In patients experiencing these symptoms, none had to discontinue treatment. The incidence of transient irritation and sneezing was approximately the same in the group of patients who received placebo in these studies, implying that these complaints may be related to vehicle components of the formulation.

Fewer than 5 per 100 patients reported headache, nausea, or lightheadedness. Fewer than 3 per 100 patients reported nasal stuffiness, nosebleeds, rhinorrhea, or tearing eyes.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

RB2-1006 March 1989

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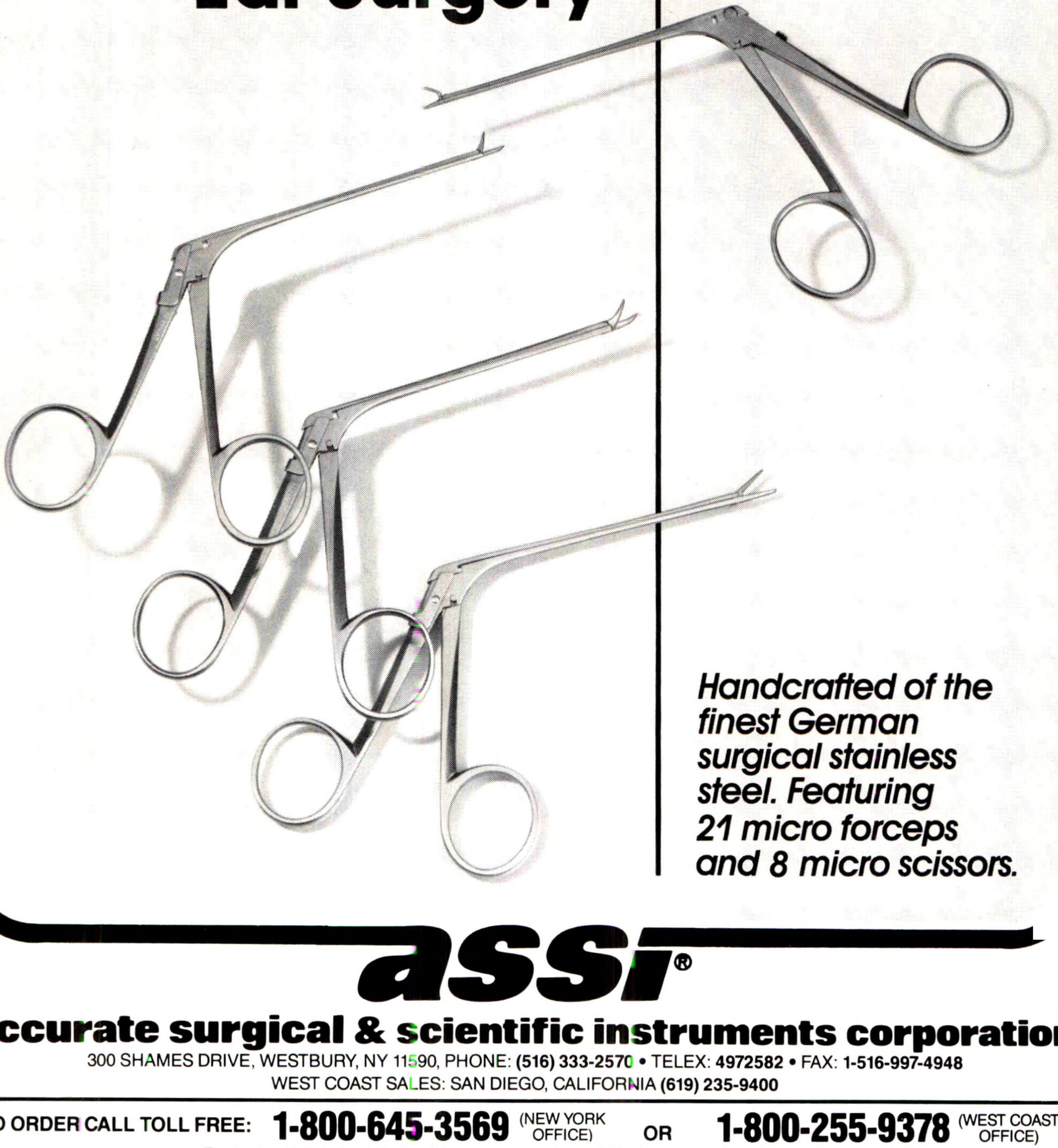

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SUPRACRICOID LARYNGECTOMY WITH CRICOHYOIDOEPIGLOTTOPEXY: A PARTIAL LARYNGEAL PROCEDURE FOR GLOTTIC CARCINOMA

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The partial horizontal supracricoid laryngectomy with cricohyoidoepiglottopexy consists of resection of the whole thyroid cartilage and paraglottic space. The cricoid cartilage, the hyoid bone, most of the epiglottis, and at least one arytenoid cartilage are conserved. Thirty-six patients with squamous cell carcinoma of the glottis who underwent this procedure from 1974 through 1986 are presented. All 36 recovered physiologic deglutition and phonation. None required a permanent tracheotomy. The 3-year actuarial survival rate was 86.5%. The local recurrence rate was 5.5%. The indications for the procedure are carcinomas of the glottis that 1) spread beyond the confines of the membranous portion of the true vocal cord or 2) present with limitation of true vocal cord mobility. The procedure is presented as a useful alternative to radiotherapy, partial vertical laryngectomy, and total laryngectomy in select cases of glottic carcinoma.

KEY WORDS — cricohyoidoepiglottopexy, glottic carcinoma, partial laryngectomy, supracricoid laryngectomy.

INTRODUCTION

There are two goals of conservation laryngeal surgery for glottic carcinoma. The first is to achieve the same local control as total laryngectomy. The second is to conserve the physiologic functions of the larynx as well as does radiotherapy.

Various partial vertical laryngectomies, based on a vertical transection of the thyroid cartilage, have been described for the treatment of glottic carcinoma.[1-8] The earliest described technique, cordectomy via a thyrotomy approach, achieves a high level of local control when the cancer is limited to the middle third of the mobile true vocal cord. Vertical hemilaryngectomy, with resection of the thyroid cartilage and paraglottic space on the tumor-bearing side, provides a safer margin than does cordectomy when the tumor extends anteriorly or posteriorly on the membranous cord. Extended vertical partial laryngectomies have been designed to address glottic carcinoma that has either spread beyond the confines of the glottis or resulted in limitation or fixation of true vocal cord mobility.

All partial vertical laryngectomies share a similar approach, which consists of vertical entry in the laryngeal lumen through the thyroid cartilage. Surgeons are aware that one of the inherent difficulties of these procedures is the "blind" entry into the larynx with a narrow field of exposure.

Vertical partial laryngectomy and its various modifications are based on the concept of compartments within the larynx separated by connective tissue barriers.[9] Experimental and clinical studies have disputed the role of connective tissue barriers as a deterrent to spread for all but the earliest glottic carcinomas.[10] Furthermore, Kirchner et al[11] have pointed out that invasion of the thyroid cartilage was more likely when the paraglottic space was invaded. Hence, the conceptual pitfall of all vertical partial laryngeal procedures is that there is only partial resection of the paraglottic space and of the thyroid cartilage, both of which may potentially be invaded by carcinoma.

The partial horizontal supracricoid laryngectomy with cricohyoidoepiglottopexy (CHEP) allows for surgical resection of glottic carcinoma, under direct vision, with wide field exposure. This procedure results in complete removal of the paraglottic space and thyroid cartilage. The preservation of mobile arytenoids results in physiologic speech and swallowing. Maintenance of the cricoid cartilage allows for decannulation. This report presents the operative technique and functional and oncologic results in 36 patients who underwent this procedure.

MATERIALS

Thirty-six patients with well-differentiated and moderately differentiated squamous cell carcinoma of the glottis were operated on from 1974 through 1986 at The University of Paris V, Paris, France.

From the Department of Otolaryngology–Head and Neck Surgery, Hospital Laennec, University of Paris V, Paris, France (H. Laccourreye, O. Laccourreye, Menard, Brasnu), and the Department of Otolaryngology–Head and Neck Surgery, The University of Iowa College of Medicine, Iowa City, Iowa (Weinstein).

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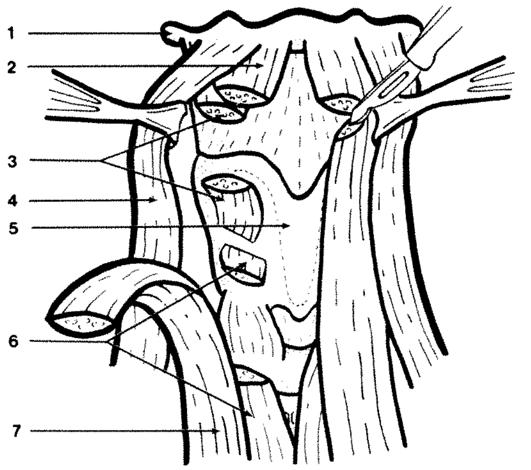

Fig 1. Transection of strap musculature. 1 — hyoid bone, 2, 6, 7 — sternohyoid muscle, 3 — thyrohyoid muscle, 4 — omohyoid muscle, 5 — thyroid cartilage. (All drawings by G.W.)

Their ages ranged from 35 to 75 years. There was a male preponderance, with 32 men and 4 women undergoing the procedure.

The staging was established according to the 1979 American Joint Committee for Cancer Staging classification. Patients with T2N0M0 tumors constituted the largest group (26/36). Among the remainder, one patient was T1aN0M0, eight were T1bN0M0, and one was T4N0M0. Eight patients had impaired mobility of the true vocal cord. One patient had impaired mobility of the true vocal cord and of the ipsilateral arytenoid. Patients with fixed vocal cords were excluded from this study.

Dysplasia and/or hyperplasia were found in the adjacent laryngeal mucosa in 50% of cases (18/36).

Twenty-six patients received preoperative chemotherapy. Cisplatin, 15 mg/m² per day, and 5-fluorouracil, 1 g/m² per day, were delivered in continuous infusion from day 1 through day 4. Three courses were given, with a 10-day hiatus between courses.

An ipsilateral functional neck dissection (sparing the 11th cranial nerve, the internal jugular vein, and the sternocleidomastoid muscle, taking node levels II to V) was performed in 50% of the cases (18/36). Postoperative radiotherapy was never performed.

The minimal follow-up in our series was 18 months. Sixteen patients were followed for at least 3 years. Actuarial survival was calculated at 3 years.

OPERATIVE TECHNIQUE

Preparation. Under general anesthesia, oroendotracheal intubation is performed. Penicillin G and metronidazole are administered intravenously. A nasogastric feeding tube (11F catheter) is inserted and a shoulder roll is placed.

Exposure. The skin incision is either a thyroidectomy type of incision or, if a neck dissection is to be performed, a U-shaped incision between the mastoid processes. A superiorly based subplatysma flap is elevated. It is imperative to raise the flap 1 cm above the hyoid bone to prevent skin retraction at the time of closure. The sternohyoid and thyrohyoid muscles are transected along the superior border of the thyroid cartilage (Fig 1). The sternohyoid muscles are then inferiorly mobilized in order to expose the underlying sternothyroid muscles and to ligate the medial laryngeal vessels (Fig 1). The sternothyroid muscles are transected along the inferior border of the thyroid cartilage, with care taken not to injure the underlying thyroid gland and vessels. The inferior pharyngeal constrictor muscles and the external thyroid perichondrium are transected along the posterior border of the thyroid cartilage lamina (Fig 2). The pyriform sinuses are released, as in a total laryngectomy, by use of a Freer elevator. The cricothyroid joints are disarticulated, with care taken not to injure the recurrent laryngeal nerves (Fig 3). The isthmus of the thyroid gland is transected and ligated.

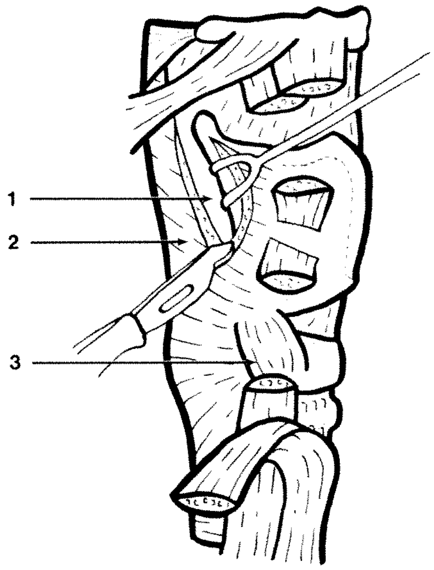

Fig 2. Transection of constrictor muscle. 1 — inner thyroid perichondrium, 2 — inferior constrictor muscle, 3 — cricothyroid muscle.

A blunt dissection is performed with a finger along the anterior wall of the cervicomediastinal trachea to the level of the carina. Care is taken to stay anterior and close to the trachea to avoid vascular injury. This step allows upward mobility of the trachea at the time of closure, eliminating tension at the suture line.

Resection. Once the exposure is completed, the larynx is entered superiorly through a transverse transepiglottic laryngotomy along the superior border of the thyroid cartilage and inferiorly through a transverse medial cricothyroidotomy along the superior border of the cricoid cartilage (Fig 4). The entire cricothyroid membrane is left attached to the

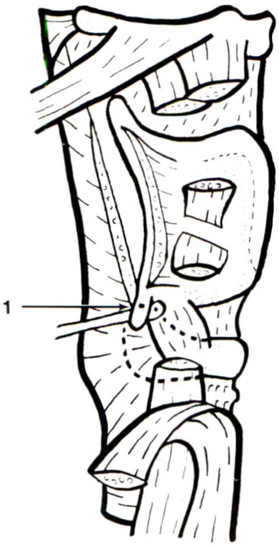

Fig 3. Disarticulation of cricothyroid joint (1).

thyroid cartilage. The oroendotracheal tube is removed and a tracheal tube is inserted via the medial cricothyroidotomy. The surgeon moves to the head of the table. The larynx is grasped with an Allis clamp and pulled inferiorly and anteriorly. The precise tumor location can now be assessed by direct visualization from above.

The endolaryngeal resection is then performed under direct vision starting on the non–tumor-bearing side. A vertical prearytenoid incision from the aryepiglottic fold to the superior border of the cricoid cartilage is performed with scissors. The pyriform sinuses and the inner surface of the thyroid perichondrium were previously elevated off the inner surface of the thyroid cartilage lamina with a Freer elevator. This first cut is made by placing one blade of the scissors in the laryngeal lumen and the other blade between the elevated thyroid perichondrium and the thyroid cartilage. The entire paraglottic space, with the specimen, is anterior to the cut, while the pyriform sinus is posterior to the cut and is therefore spared (Fig 5).

The vertical prearytenoid incision and the medial transverse cricothyroidotomy are then connnected on the non–tumor-bearing side with an incision that transects the cricothyroid muscle and the main part of the lateral cricoarytenoid muscle along the superior border of the cricoid cartilage. The thyroid cartilage is then gripped between the surgeon's hands and broken forward along the midline as if the surgeon is opening a book. The fracture allows for complete visualization of the tumor-bearing side, which has not yet been transgressed (Fig 6).

Excision of the tumor is then performed under direct vision with use of a horizontal incision along the superior border of the cricoid cartilage and a vertical prearytenoid incision. It is important to emphasize that if necessary, this procedure allows for partial or total removal of the arytenoid cartilage on the tumor-bearing side. Furthermore, partial resection of the anterolateral portion of the cricoid cartilage is also possible.

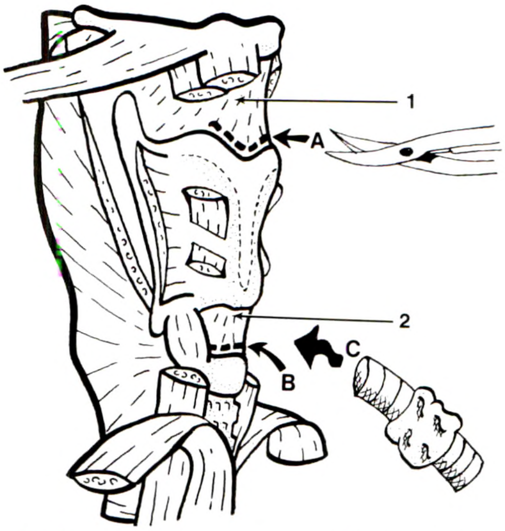

Fig 4. Exposure of larynx. 1 — thyrohyoid membrane, 2 — cricothyroid membrane, A — transepiglottic laryngotomy, B — cricothyroidotomy, C — placement of endotracheal tube.

Closure. The mucosa of only the upper part of the arytenoid cartilages is sutured (4-0 Vicryl suture) to cover the exposed cartilage. The inferior portion of the arytenoid is left unsutured. If one arytenoid cartilage has been removed, no attempt should be made to cover the raw surfaces. Each remaining arytenoid cartilage is then pulled forward to the posterolateral part of the cricoid cartilage, with a 2-0 Vicryl suture, to avoid posterior rotation of the arytenoid cartilages.

Impaction of the hyoid bone to the cricoid cartilage is then performed. Three submucosal 0 Vicryl sutures are looped around the cricoid cartilage,

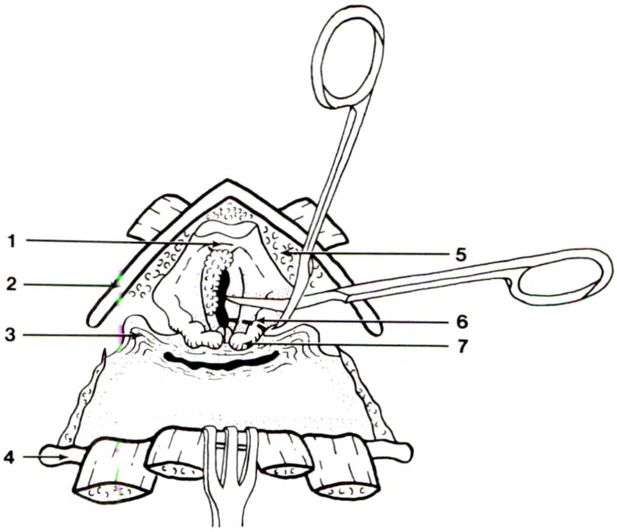

Fig 5. Superior view of larynx. 1 — epiglottis, 2 — thyroid cartilage, 3 — pyriform sinus, 4 — hyoid bone, 5 — paraglottic space, 6 — prearytenoid incision, 7 — arytenoid cartilage.

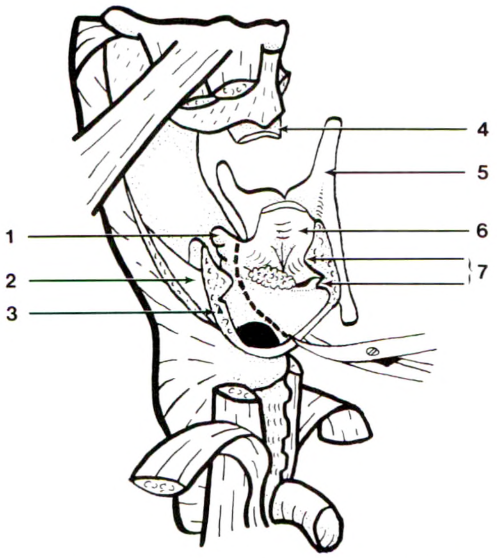

Fig 6. Final resection margin. 1 — arytenoid cartilage, 2 — inner thyroid perichondrium, 3 — vocal process, 4 — epiglottis and preepiglottic space, 5 — thyroid cartilage, 6 — petiole, 7 — false and true vocal cords.

passed through the remaining epiglottic cartilage, and looped around the hyoid bone (Fig 7). The first suture is placed at the midline. The other two sutures are set bilaterally 0.5 cm from the midline. The sutures are then pulled together to allow the previously released cervicomediastinal trachea to move upward. At this point a tracheotomy is performed through the original skin incision to allow for ventilation while the closure is performed. The three sutures are cinched tightly, with care taken to leave no gap between the cricoid cartilage and the hyoid bone. Furthermore, the anterior borders of the hyoid bone and cricoid cartilage must be carefully aligned. The previously sectioned sternohyoid muscles are sutured with 3-0 Vicryl sutures. One or two suction drains are inserted into the wounds. Skin closure is performed in two layers. The cuffed endotracheal tube is replaced by a cuffless tracheotomy tube, and a dressing is applied.

Postoperative Care. Penicillin G and metronidazole are continued postoperatively. The metronidazole is stopped on day 10. Penicillin is given until removal of the nasogastric feeding tube. The tracheotomy tube is removed as soon as possible, the first attempt being made by postoperative day 3. Respiratory and speech therapists are involved in the postoperative rehabilitation of the patient. The surgeon must encourage the patient to practice swallowing secretions by day 10. When the patient is capable of swallowing saliva he or she is started on a "supraglottic diet." Once the patient tolerates this diet, liquids are introduced and the nasogastric tube is removed.

RESULTS

ONCOLOGIC RESULTS

Survival. The 3-year actuarial survival rate was 86.5%. The causes of the three deaths were distant metastasis, second primary disease, and intercurrent disease, respectively.

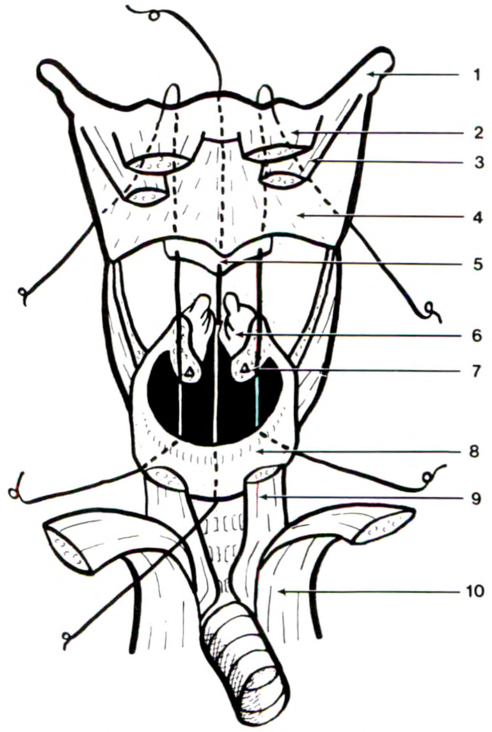

Fig 7. Closure. 1 — hyoid bone, 2, 10 — sternohyoid muscle, 3 — thyrohyoid muscle, 4 — thyrohyoid membrane, 5 — epiglottis and preepiglottic space, 6 — arytenoid cartilage, 7 — vocal process, 8 — cricoid cartilage, 9 — sternothyroid muscle.

Local and Cervical Recurrence. The overall local recurrence rate was 5.6% (2/36). Both recurrences were T2N0M0 (7.7% or 2/26). The local recurrences were noted during the first postoperative year and were successfully managed by surgical salvage.

The overall neck recurrence rate was 8.4% (3/36). None of these patients underwent elective lymphadenectomy at the time of primary resection. Among 18 patients who underwent elective lymphadenectomy, no positive nodes were identified.

Preoperative chemotherapy did not significantly affect the rates of local or cervical recurrence.

FUNCTIONAL RESULTS

Respiration. All patients were decannulated. The average time until decannulation was 7 days, ranging from 3 to 57 days.

Deglutition. The nasogastric tube was left in place, on average, for 15 days, ranging from 9 to 30 days. All of the patients recovered normal swallowing without weight loss or pneumonia from aspiration. Deglutition was achieved by the first postoperative month in 97% (35/36) of the cases.

Phonation. Physiologic phonation was achieved by all patients. Thirty-five patients were phonating within the first postoperative month. The quality of the postoperative voice allowed for normal social interaction. The postoperative voice tended to be breathy and might be compared to that of a patient with chronic laryngitis.

Extended Cartilaginous Resections. One patient required a cricoarytenoid disarticulation with arytenoid cartilage resection in order to obtain clear surgical margins. This patient was decannulated by day 7. The nasogastric feeding tube was removed by day 19. No complications were encountered.

One patient in our series had a resection of the anterolateral portion of the cricoid cartilage. The patient was decannulated by day 3 without complications. This procedure should be called a partial horizontal supracricotracheal laryngectomy with cricotracheohyoidoepiglottopexy.

COMPLICATIONS

No infectious complications were noted. One patient with a history of severe vasculitis did, however, have progressive necrosis of the hyoid bone over a period of 2 months. This complication was managed expectantly. Neither surgical treatment nor tracheotomy was required.

DISCUSSION

In 1959, Majer and Rieder[12] published the first description of a partial laryngeal resection for carcinoma in which the final reconstruction was accomplished by suturing the hyoid bone to the cricoid cartilage. The procedure was refined further by Labayle and Bistmuth[13] in 1971 and Piquet et al[14] in 1974. Some confusion over nomenclature exists. The literature is replete with names for this procedure, such as reconstructive laryngectomy and total laryngectomy with reconstruction. These names do not fully describe this procedure, in which the superior two thirds of the epiglottic cartilage, the hyoid bone, and one or both of the arytenoid cartilages are preserved. It is the authors' opinion that the name partial horizontal supracricoid laryngectomy best describes the surgical approach and resection, while the acronym CHEP explains the mode of reconstruction. The term is shortened to supracricoid laryngectomy with CHEP.

All patients in this series were decannulated. The average time until decannulation was 7 days. This was facilitated by maintaining the circumferential integrity of the airway by impacting the hyoid bone to the cricoid cartilage. Nonetheless, our experience has shown that the anterolateral portion of the cricoid cartilage may be resected if necessary. Tracheohyoidopexy is then performed by impacting the trachea to the hyoid bone.

It is our opinion that a noncuffed tracheostomy tube should be placed at the end of the procedure. This appears to preserve an active cough reflex from the earliest postoperative period onward. It also may reduce peristomal soft tissue infection, tracheitis, and localized tracheomalacia. The tracheotomy tube should be removed early in the postoperative period; the first attempt is made by day 3. This results in early closure of the tracheostoma, arytenoid cartilage mobilization, and physiologic upward ascent of the larynx during deglutition, all of which aid in the rehabilitation of the swallowing mechanism.

Early resumption of physiologic swallowing was the rule in this population. The functional results were similar to those reported in other European series.[15,16] Sparing both the recurrent laryngeal and the superior laryngeal nerves bilaterally maintains the sensation and mobility of the remaining laryngeal structures. The recovery of laryngeal sphincteric function is achieved by active apposition of the arytenoid cartilages with the suprahyoid epiglottic cartilage and the base of the tongue. Postoperative videostroboscopy reveals the formation of a transverse neoglottic chink replacing the normal anteroposterior lumen between the vocal cords. Cricopharyngeal myotomy is never performed. In the authors' opinion this disturbs the hypopharyngeal phase of deglutition and may predispose the patient to gastroesophageal reflux.

The application of certain pathologic techniques, such as whole organ sectioning, has elucidated the pathways of carcinomatous spread in the larynx. A number of studies have emphasized that early glottic carcinomas frequently invade the anterior commissure.[11,17] With increasing size the cancer has a tendency to invade the paraglottic space; thyroid cartilage invasion is more likely once the paraglottic space is invaded.[18,19] Furthermore, clinicopathologic studies have revealed that the main cause for fixed or impaired mobility of the true vocal cord is thyroarytenoid muscle invasion.[20,21] There is clearly a need for a partial laryngectomy that avoids a medial cut through the thyroid cartilage yet results in total removal of the paraglottic space, anterior commissure, and thyroid cartilage. Partial horizontal supracricoid laryngectomy with CHEP best meets these requirements. We do believe that for early glottic carcinomas confined to the unilateral membranous true vocal cord, vertical partial laryngectomy remains a viable option.

The observation that none of the T1b and only 7.7% of the T2 glottic carcinomas in this series recurred locally has allowed us to define when the partial horizontal supracricoid laryngectomy with CHEP is best indicated:

1. Bilateral T1 glottic carcinomas with or without anterior commissure involvement.
2. Unilateral T1 glottic carcinomas with anterior commissure involvement.

3. T1 glottic carcinomas with various areas of dysplasia or hyperplasia.
4. Unilateral or bilateral T2 glottic carcinomas with or without impaired mobility of the true vocal cord.

This series does not include any T3 lesions; however, it is our opinion that a partial horizontal supracricoid laryngectomy with CHEP should be attempted in cases in which the ipsilateral arytenoid is mobile and the preepiglottic space is not involved. More extensive T3 lesions may require either a near-total laryngectomy as described by Pearson et al[8] or a total laryngectomy.

The main contraindications to the partial horizontal supracricoid laryngectomy with CHEP are the following.

1. Lesions originating in the ventricle or anterior commissure, since these have a propensity for early involvement of the preepiglottic space.
2. Ipsilateral arytenoid cartilage fixation. Such tumors invade the cricoarytenoid joint, the posterior cricoarytenoid muscles, or the posterior portion of the cricoid cartilage.
3. Subglottic extension more than 10 mm anteriorly and 5 mm posterolaterally, as these tend to involve the cricoid cartilage.
4. Preoperative respiratory impairment.

There are no age-related contraindications, but care must be used when considering patients in the over-70 age group, especially if gastroesophageal reflux is present.

CONCLUSIONS

The partial horizontal supracricoid laryngectomy with CHEP allowed for physiologic rehabilitation, without tracheotomy, of all 36 patients in this report.

It is our opinion that this procedure should be performed when glottic carcinoma has spread beyond the confines of the membranous true vocal cord and/or presents with impaired mobility of the true vocal cord. In such cases our series achieved an overall local recurrence rate of 5.5%, which is lower than has been reported for partial vertical laryngectomy. Studies are presently under way to assess the efficacy of this procedure in cases of glottic carcinoma with fixed true vocal cords and/or after radiotherapy.

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OTITIC CANDIDIASIS IN CHILDREN: AN EVALUATION OF THE PROBLEM AND EFFECTIVENESS OF KETOCONAZOLE IN 10 PATIENTS

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The purpose of this paper is to report a group of children with recurring ear infections in whom persistent otorrhea was found to be due to monilial (*Candida*) infection of the middle ear. Some of the patients had associated mastoid disease. A review of the literature reveals few reports of otitis media and/or mastoiditis due to *Candida* infection. Ten patients who had persistent otorrhea were found to have monilial infection as a cause of the ear disease. None of the patients were immunosuppressed or immunocompromised. Nine of the 10 patients (one was lost to follow-up) were treated with antifungal medication, and the effectiveness of ketoconazole therapy is evaluated. None of the children in this series had systemic candidiasis. The probable causes of the problem of yeast infection of the ear are explored and appear to be related to the use of multiple broad-spectrum antibiotics and local antibiotic-steroid ear drops.

KEY WORDS — candidiasis, fungal otitis media, ketoconazole, mastoiditis.

INTRODUCTION

Ubiquitous, often harmless, and fortunately rarely fatal, fungal disease is occurring in the human with increasing frequency. With the increased number of patients who have immunosuppression, immunodeficiencies, leukemia, malignant tumors, and diabetes, and patients who are treated with anticancer drugs and steroids, larger numbers of humans are especially vulnerable to fungal invasion. The use of antibiotics can cause overgrowth of some fungal diseases, most commonly *Candida*, even in the absence of immunodeficiency or systemic immunosuppression. Fungal disease may create a high degree of morbidity or may even be fatal, so early recognition and active therapeutic measures to control the disease are of extreme importance.

Fungal disease of the external ear canal is well documented, especially in certain climates and under certain conditions. However, it has rarely been reported as an etiologic agent of disease in the middle ear and mastoid.

While there have been increasing numbers of children with systemic candidiasis, it is surprising that reports of involvement of the middle ear and temporal bone have not appeared in the literature. Mucocutaneous candidiasis is known to occur in immunosuppressed and immunodeficient children, yet the ear has not been reported as an area of involvement even when systemic candidiasis exists. Since *Candida* infections of the oropharynx, gastrointestinal tract, and genitourinary tract have been known to occur in normal children who are treated with multiple antibiotics, the ear certainly must be vulnerable to its invasion. This paper presents 10 children with recurring otitis media who were treated with ventilation tubes. These children had recurrent ear infections that were treated with multiple broad-spectrum antibiotics and local steroid-antibiotic drops, and they presented with persistent otorrhea found to be due to *Candida*. The response to ketoconazole therapy is evaluated. Some of the children required mastoid operations.

LITERATURE REVIEW

McLellan et al[1] reported what they believed to be the first case of *Candida* otitis media in a newborn infant. Fungal infections of the middle ear and mastoid have been reported in older children, but have not been due to monilial disease. Bodey and Fainstein,[2] in an extensive review on candidiasis, found it to be a frequent problem in the oropharynx and vagina and believe that disseminated candidiasis is a disease of medical progress. The occurrence of this disease is more common when two or more antibiotics have been used for previous bacterial infection. *Candida* can infect any organ system in the body, yet no mention is made in this study of otitis media. Keller et al[3] indicate that *Candida* can be cultured from the mouth and the pharynx of newborns and is ubiquitous in the infant age group, yet they do not mention the ear as an area of involvement.

Falser[4] points out that mycotic infections of the auditory canal and middle ear occurred in patients who were at high risk because they had extensive ear operations, immunosuppression, long-term antibiotic therapy, or organ transplantation. Chelidze[5] examined a total of 134 patients 1 to 15 years of age with inflammatory disease of the ear, and fungal otitis media was found in only 7 of the pa-

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TABLE 1. PATIENT DATA

				Insertion of Tubes		*Otorrhea*		
Pt No.	*Age When First Seen*	*Sex*	*Age at Onset of Ear Disease*	*Age at First Insertion*	*No. of Times*	*With Tubes*	*Before Tubes*	*Duration*
1	9 mo	F	2 wk	9 mo	1	M bilat	+	2 yr
2	4 yr 9 mo	M	3 yr 6 mo	6 yr	1	M bilat	+	2 mo
3	1 yr 1 mo	M	7 mo	2 yr 2 mo	1	M bilat	–	1 wk
4	1 yr 1 mo	F	5 mo	1 yr 2 mo	1	M bilat	+	4 mo
5	3 yr	M	1 yr	3 yr 3 mo	1	M unilat	–	1 mo
6	3 yr 9 mo	M	3 yr	1) 4 yr 8 mo 2) 6 yr 1 mo	2	M bilat	–	3 wk
7	1 yr	M	7 mo	1 yr 3 mo	3	M bilat	–	3 mo
8	4 yr	M	Unknown	1) 4 yr 1 mo 2) 5 yr 3 mo 3) 7 yr 10 mo	3	M bilat	–	4 mo
9	2 yr 6 mo	F	3 mo	2 yr 2 mo	2	First set none, second set unilat	–	1) None 2) 6 mo
10	2 yr 6 mo	M	2 wk	2 yr 6 mo	2	M bilat	–	Cont P/O

All patients received topical steroid-antibiotic ear drops and multiple antibiotics.

M — multiple, S — spontaneous, bilat — bilateral, unilat — unilateral, Cont P/O — continuously postoperatively.

tients. Buchs[6] evaluated *Candida* meningitis as a growing threat to the premature and full-term infant and found only 1 of the patients of the series had mastoiditis. Klein et al[7] state that the use of steroids and antibiotics suppresses normal flora and encourages growth of fungus such as *Candida albicans*.

Meyerhoff et al[8] reported three cases of candidiasis of the inner ear in adult patients and state that this kind of mycotic infection of the inner ear has rarely been reported. At postmortem temporal bone studies, they found a focus of *Candida* sp in the vestibule under the stapedial footplate without apparent involvement of the internal auditory canal. Symoens and Cauwenbergh[9] report the use of ketoconazole as a new step in the management of fungal disease. The authors state that antimycotic drugs have developed in the shadow of antibiotic therapy. Ketoconazole is the first antimycotic that is broad-spectrum, effective orally, and well tolerated. This drug shows activity against a wide range of fungal organisms. Ketoconazole in low concentrations produces changes in the cell wall of *C albicans*, increases the cell volume, and causes abnormalities of cell division. At higher concentrations it produces membrane breakdown and distortion in the shape of the cell. At doses of 50 μg/mL, cell necrosis occurs. Data are available that suggest that the development of fungal drug resistance is not likely to be a problem with ketoconazole. Administration of this drug with food appears to result in higher plasma concentrations than when the drug is taken in a fasting state.

Falser[10] in 1984, in a paper on fungal infections of the ear, reported involvement of the auditory canal and middle ear as being left unnoticed and regarded as a harmless saprophytic growth. However, these infections, he points out, may become clinically significant in patients undergoing long-term or repeated antibiotic therapy. Horsburgh and Kirkpatrick[11] conclude that ketoconazole is an effective and well-tolerated drug for the treatment of an infectious component of chronic mucocutaneous candidiasis. Adverse reactions were infrequent.

METHOD

All of the 10 patients had persistent and prolonged otorrhea, either unilateral or bilateral, in spite of multiple antibiotics and corticosteroid-antibiotic ear drops. In every patient, the aural discharge pulsated from the middle ear through the ventilation tube. The purulence from the middle ear was obtained for culture either by suctioning the discharge from the middle ear through the tube or by the use of a calcium alginate swab placed onto the pulsating discharge from the tube. The specimen was immediately placed into a holding medium and sent to the laboratory for Gram's stain, fungal stain, routine cultures, and fungal cultures. An additional request was made for sensitivity tests to be done on all pathogens, whether bacterial or fungal.

To ensure that the fungus was not a contaminant from the external canal in children treated with multiple broad-spectrum antibiotics and ear drops, the charts of 97 patients with otorrhea, treated in the same fashion as those children with *Candida* infection, were reviewed. In none of these patients were fungi found in the cultures or Gram's stains.

One can conclude that *Candida* or fungus is not a normal finding in the child with otorrhea, and the only difference noted in the children who had positive fungal cultures was the duration of the aural drainage or the need for multiple courses of antibiotics. It should be reinforced that in all patients with otorrhea following use of ventilation tubes, the bacterial cultures were always positive. As will be seen in the results and patient information, the *Candida* infection may also be found in the middle ear when a myringotomy was performed on an in-

TABLE 2. FINDINGS AND THERAPY

Pt No.	*Mastoiditis on Radiograph*	*Mastoid Operation*	*Sinusitis*	*Bacterial Cultures*	*Ketoconazole Therapy*	*Duration of Therapy*
1	C, bilat	Bilat x6*	+ (F)	+	+	3 d
2	None	None	+ (NF)	+	+	2 wk 3 d
3	C, bilat	Bilat simple	–	+	+ (x2)	1) 5 d 2) 1 mo
4	None	None	–	–	+ (x2)	1) 2 wk 2 d 2) 1 mo
5	C, unilat	Unilat simple	+ (NF)	+	+	2 mo
6	None	None	+ (NF)	+	+	3 wk
7	C, bilat	None	+ (NF)	+	+	3 wk
8	None	None	–	+	+	6 wk
9	C, unilat	Unilat simple	–	+	+	1 mo
10	C, bilat	None	+ (NF)	+	–	None

Patient 1 (only) has had amphotericin B and flucytosine therapy (x2).

C — coalescent, F — cultured positive for fungi, NF — no fungi on culture.

*Last operation was bilateral modified radical.

fected ear with an intact drum. The 97 patients in the control group whose charts were reviewed were seen during the period of this study.

EVALUATION OF PATIENT DATA

A composite of details of the 10 patients in this study is presented in Tables 1-3 and will be summarized.

From Table 1 it can be seen that of the 10 patients, 3 were female and 7 were male. The youngest child was 9 months of age and the oldest was 4 years 9 months of age when first seen. In these patients, the age at onset of the ear infections ranged from 2 weeks to 3½ years of age. In 1 patient, the onset of the ear disease could not be determined. The age at which ventilation tubes were inserted ranged from 9 months to 6 years of age. Of these patients, 5 had ventilation tubes more than once, and some had as many as three sets of tubes. In most of the patients, otorrhea, either unilateral or bilateral, occurred many times and ranged in duration from 1 week to 4 months. In 1 patient, otorrhea persisted with only a short period of respite (3 months of respite on one occasion) and continued for a period of over 2 years (patient 1). This patient still has otorrhea at the writing of this paper. Every patient had local topical steroid-antibiotic drops that were used repeatedly. Otorrhea occurred spontaneously in 3 of the patients prior to tube insertion, 2 of whom had mastoiditis. Every patient required treatment with many broad-spectrum antibiotics.

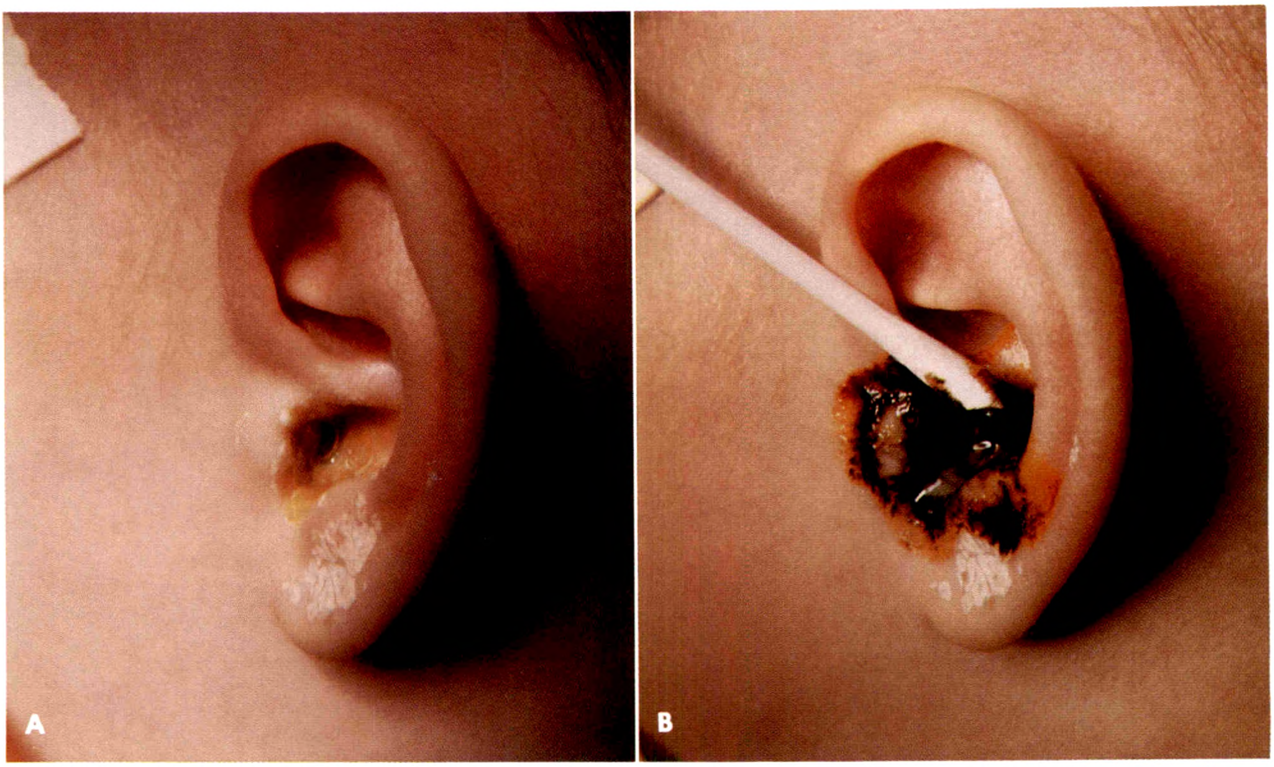
From Table 2 one can glean the following information. There was radiographic evidence of mastoiditis in 6 of the children: bilateral in 4 and unilateral in 2. Radiographic findings were normal in 4 patients. Mastoidectomy was necessary in 4 patients: bilateral in 2 and unilateral in 2. Three of the children had simple mastoidectomies, and 1 (patient 1) had bilateral simple mastoidectomies six times. Her last operation was a bilateral modified radical mastoidectomy. Six of the children with chronic rhinorrhea presented with radiographic evidence of sinusitis, only 1 of whom (patient 1) had a positive culture for *C albicans*. In 9 of the 10 patients, bacterial infection, either anaerobes or aerobes, was found.

All of the patients except 1 (patient 10) were treated with ketoconazole, 2 of whom had two courses of therapy. The duration of therapy with this antifungicide varied from 3 days to 6 weeks. It was only patient 1 who could not tolerate the medication. Amphotericin B and 5-fluorocytosine were necessary only in patient 1.

TABLE 3. OUTCOME

Pt No.	*Side Reactions to Ketoconazole*	*Fungus Species on Culture*	*Immunologic Status If Tested*	*Period of Follow-up*
1	Vomiting, diarrhea	*Candida luisitania*	Normal	2 yr
2	None	*Penicillium, Aspergillus*	Normal	1 yr
3	None	*Candida albicans*	Normal	2 yr
4	Sleeplessness, but none when drug resumed	*Candida albicans*	Not examined	5 mo
5	None	*Candida parapsilosis*	Not examined	4 yr
6	None	*Candida albicans, Aspergillus*	Normal	3 yr
7	None	*Candida albicans*	Not examined	2 yr
8	None	*Candida parapsilosis*	Not examined	1 yr
9	None	*Candida parapsilosis*	Normal	4 yr
10	No ketoconazole	*Candida albicans*	Normal	Lost to follow-up

On audiologic evaluation, all children were judged to have impaired hearing before therapy and normal hearing after therapy.



(Patient 1) A) Photograph of ear, taken at time of first mastoidectomy. B) Ear as it appeared after being prepared with Betadine (positive starch reaction).

Table 3 shows the following patient information. All of the children in the study had slight to moderate conductive hearing loss at the onset of their disease. The hearing returned to normal in every child. Ketoconazole was well tolerated in all of the patients except patient 1, who developed diarrhea and vomiting. In 1 patient (patient 4), the drug was stopped after 3 days because of sleeplessness; because the otorrhea recurred, the drug was resumed and was well tolerated. The fungus cultures from the ears showed *C albicans* in 5 of the children, *Candida parapsilosis* in 3 of the patients, *Candida luisitania* in 1 patient, *Aspergillus* in 2 patients, and *Penicillium* in 1. The immunologic evaluations performed in 6 of the 10 patients yielded normal results. The period of follow-up of 9 of these patients ranged from 5 months to 4 years; 1 of the patients was lost to follow-up, having moved out of the area.

CONCLUSIONS

This is a retrospective study of 10 patients who developed fungal disease of the middle ear and/or mastoid. Fungal disease of the ear has generally been assumed to be due to external canal involvement or contamination. Candidiasis of the middle ear or temporal bone has rarely been reported. It is probably more frequent than the literature would reflect. The children in this series did not have any of the high-risk factors that cause fungal invasion in humans, except for the use of multiple broad-spectrum antibiotics.

It is difficult to comprehend the lack of reports of temporal bone involvement in infants and children. Although *Candida* infection has been extensively reported in every other organ of the body, even in patients with systemic disease, involvement of the ear remains heretofore relatively unreported. The true incidence of fungal disease in patients with chronic otorrhea or chronically recurring otitis media treated with multiple broad-spectrum antibiotics and local steroids and antibiotic medication is unknown.

The literature was reviewed, and it is of interest that in patients with fungal meningitis, autopsy examination failed to reveal any evidence of disease within the middle ear or mastoid.

All of the children in this series had protracted otorrhea, many for weeks to months, that was treated with antibiotics and failed to clear. None of the children in this series developed any destructive process of the otic capsule. Neither the fungus nor its toxins produced inner ear disease. It is unknown whether *Candida* can produce permanent damage of the temporal bone in children who are immunosuppressed or immunodeficient. There was no evidence, either clinically or at surgical exploration, that any of the patients in this series had ossicular necrosis. The histologic reaction of the mastoid bone in patient 1, which led to a pathologic diagnosis of histiocytosis X, was most likely due to a tissue reaction caused by fungal infection. The child did not have reticuloendotheliosis, as all the tests for this disease were negative.

In patients who tolerated this drug, the response to ketoconazole was remarkable. The persistent otorrhea, in many instances over a period of weeks to months, was rapidly controlled. Ketoconazole appeared to be fairly nontoxic in this group of patients. There was no evidence of emergence of drug resistance, since on two occasions two courses of medication were necessary and the response was excellent. None of the patients had oral thrush. All of the patients who were treated with ketoconazole tolerated the medication well, except for patient 1.

Liver function tests were not performed because therapy with the antifungicide was of such short duration. The duration of therapy was gauged by clinical response to the ketoconazole. In most of the patients, control of otorrhea occurred within a very short period of time. The use of antibiotics in those patients with both fungal and bacterial infection did not diminish the effectiveness of ketoconazole in controlling the monilia.

When bacterial cultures are negative in patients with protracted otorrhea, a search for fungal infection should be instituted. The common denominators in this group of patients with fungal otitis media and/or mastoiditis were as follows: 1) repeated treatment with multiple broad-spectrum antibiotics, 2) usually, the presence of ventilation tubes, 3) the local use of steroid-antibiotic drops, and 4) multiple episodes of prolonged otorrhea requiring antibiotic therapy. While ketoconazole effectively eliminated the fungal involvement of the middle ear and mastoid in 8 of the 10 patients in this series, it should not be used in children with bony invasive disease.

The Figure, A, is a photograph of the ear of patient 1 taken at the time of the first mastoidectomy. The Figure, B, shows the child's ear as it appeared after being prepared with Betadine (a positive starch reaction).

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CORRECTION

In the article by Yanagisawa et al (Role of the Soft Palate in Laryngeal Functions and Selected Voice Qualities. Simultaneous Velolaryngeal Videoendoscopy, *Ann Otol Rhinol Laryngol* 1990;99:18-28), two lines from the last sentence beginning on page 20 were inadvertently omitted. The complete sentence should read, "The audio signals were simultaneously recorded on all cassettes via a single microphone held by the subject."

Ann Otol Rhinol Laryngol 99:1990

VELAR-PHARYNGEAL STATUS IN CLEFT PALATE PATIENTS WITH EXPECTED ADENOIDAL INVOLUTION

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This study was designed to provide information about whether cleft palate patients with hypertrophied adenoids maintain velar-pharyngeal contact during the time of expected adenoidal atrophy. Thirty-nine subjects were selected from a large longitudinal study on the basis of availability of lateral still x-ray films taken in series from 5 to 16 years of age. Ratings of velar-pharyngeal contact and ratings of adenoid size were obtained from the films. The obtained data indicated the expected decrease in adenoid size but also, for the group, maintenance of velar-pharyngeal contact. However, three of the 39 subjects were judged to show loss of such contact during the period of study, and an additional four had surgery for velopharyngeal incompetence after the completion of the study. All seven appeared to show significant deterioration of velopharyngeal status in middle or late adolescence. Implications of these findings are discussed.

KEY WORDS — adenoidal atrophy, cleft palate, velar-pharyngeal status.

INTRODUCTION

As indicated by Subtelny and Koepp-Baker[1] as well as others, it seems likely that an enlarged adenoidal pad may facilitate velopharyngeal function by decreasing the distance, mainly in the anteroposterior dimension, between the velum and the pharyngeal wall. This "assistance" might be particularly useful when the patient has a shortened palate, a palate of decreased mobility, or a nasopharynx that is excessively deep, all of which may occur in patients with cleft palate or congenital palatal incompetence.

As a consequence, clinicians sometimes find these patients to have normal or relatively normal nasalization of speech before adenoidectomy and moderate or severe nasalization of speech afterward. We can infer from this observation that the patient had normal or nearly normal velopharyngeal function before surgery, but that closure of the nasopharyngeal port during speech was no longer possible after adenoidectomy. Indeed, frequently congenital palatal incompetence is not discovered until after adenoidectomy.[2]

In contrast, clinical experience indicates that the patient with normal oral, palatal, and pharyngeal structures may show increased nasalization immediately following adenoidectomy but a rapid return to normal voice, perhaps even within 24 hours.

An important question is whether there is an increase in nasalization and a decrease in efficiency of velopharyngeal function in patients with cleft palate with normal involution of adenoidal tissue.

Not much information is available about this question. The relationships among oral pharyngeal structures, including the adenoids, were identified in two important early papers by Ricketts[3] and by Subtelny and Koepp-Baker.[1] In the latter paper, the authors provided some of the first published findings about the relationships between size of adenoidal tissue and velopharyngeal function. They reported longitudinal cephalometric data for several patients and concluded with a discussion about the importance of maintaining adenoid tissue in children with cleft palate. Later, both Greene[4] and Gibb[5] reported clinical studies that indicated the significance of adenotonsillectomy in causing hypernasal speech in certain children. Schweiger[6] and Calnan[7,8] indicated the relative importance of nasopharyngeal depth in velopharyngeal function. Mason[9] and Morris[10] offered some suggestions about the role of adenoids in velopharyngeal function, particularly regarding clinical management. Morris et al[2] reported some retrospective data about early identification of congenital palatal incompetence, a diagnosis frequently made only following adenoidectomy.

More relevant is the paper by Mason and Warren,[11] in which the authors reviewed the case for a concern about "developing hypernasality in cleft palate" with adenoid involution. They also presented two cases in which increased nasalization of speech was observed over time, accompanied by aerodynamic data that indicated deterioration of velar-pharyngeal function. In both cases, the deterioration of velopharyngeal function could be accounted for by adenoidal involution.

We reported some findings that are relevant, indirectly, to the issue in a previous paper.[12] In that study we classified 131 cleft palate children at an early age (before 6 years) by clinical composite ratings of velopharyngeal competence (competent,

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TABLE 1. DESCRIPTION OF X-RAY FILM DATA (N = 39)

	Mean	*SD*	*Range*
Age in years at first film	5.44	0.50	5- 6
Age in years at last film	13.78	1.79	10-17
Number of years studied	8.33	1.66	5-11
Number of films	7.28	1.68	4-11

marginal, incompetent) and reported these clinical ratings, speech articulation test scores, and ratings of connected speech for each of the three groups through the age of 16 years. Presumably this age period (6 through 16) is that during which adenoidal involution normally occurs. Fifty-one of the 131 subjects were judged by the criteria used in that study to demonstrate velopharyngeal competence for speech at or before age 6. Of the 51 subjects, 73.5% maintained that status over the period of study. The remaining 26.5% were classified as showing marginal velopharyngeal status by the age of 16 years. Two of the latter group received secondary physical management (pharyngeal flap or Teflon injection).

Fifty of the 131 subjects were judged initially to show marginal velopharyngeal competence; of that 50, 15 developed nasalization of speech sufficiently severe to merit secondary physical management.

Thirty of the 131 subjects initially showed velopharyngeal incompetence; 28 of the 30 continued to merit that classification and received secondary physical management (mainly pharyngeal flap) during the study period.

These findings seem to indicate general stability of velopharyngeal function but that, indeed, some patients, particularly those with marginally satisfactory function, may show deterioriation of function during this age period, presumably in part by reason of adenoidal atrophy.

Additional information about the problem was reported by Siegel-Sadewitz and Shprintzen[13] in their study of changes in velopharyngeal valving with age. They used endoscopy to describe the velopharyngeal mechanism in 20 normal and ten cleft palate subjects observed over a 10-year period. Among their several questions was one about changes in physiologic valving patterns with any structural changes associated with adenoid involution. Not many details are provided about the procedure used; evaluations apparently were made by a panel of experienced diagnosticians, with attention to closure patterns and movement patterns of the various velopharyngeal structures. They report that "in no instances did velopharyngeal insufficiency develop following adenoid involution for either the normal or cleft subjects."(p 173)

The purpose of the present investigation is to provide some additional information about the question of whether velopharyngeal status deteriorates in cleft palate children with adenoidal atrophy. Specifically, lateral cephalometric films for cleft palate subjects were inspected to determine whether adenoid size decreases with age and whether midline approximation between the soft palate and the posterior pharyngeal wall is lost over time as the adenoids atrophy.

TABLE 2. NUMBERS OF SUBJECTS FOR WHOM FILM WAS AVAILABLE AND MEAN RATINGS OF VELAR-PHARYNGEAL CONTACT STATUS AND ADENOID SIZE BY AGE

		Velar-Pharyngeal Contact Rating		*Adenoid Size Rating*	
Age	*No. of Subjects*	*Mean*	*SD*	*Mean*	*SD*
5	20	1.95	1.43	2.10	0.55
6	34	2.12	1.34	2.26	0.79
7	31	1.84	1.11	2.00	0.63
8	31	1.52	0.89	2.32	0.65
9	31	1.90	1.14	2.13	0.72
10	26	1.77	0.95	2.08	0.74
11	28	2.00	1.38	2.18	0.82
12	24	1.75	1.15	2.13	0.85
13	24	2.20	1.31	1.96	0.86
14	16	2.31	1.35	1.81	0.91
15	11	2.27	1.19	1.64	0.81
16	12	2.25	1.29	1.67	0.78
17	3	2.00	1.00	1.67	1.15

METHODS

Subjects. Subjects were selected from a large clinical population for whom serial lateral still cephalometric films are available and who 1) demonstrated adenoid tissue judged to be enlarged by film inspection between ages 5.0 and 7.0 years, 2) showed approximation of velar and pharyngeal structures by the same film, and 3) had at least four serial annual films of readable quality during a 5-year period subsequent to the initial film. No subject could have adenoidectomy or secondary surgery for velar-pharyngeal dysfunction during the period of study. Subjects were not selected by sex, cleft type, or type or age of palatoplasty.

Thirty-nine subjects qualified for the study. Of the 39, 22 were boys and 17 were girls. Nine subjects had bilateral clefts of the lip and palate, 21 had unilateral clefts of the lip and palate, four subjects had clefts of the hard and soft palates, and five had clefts of the soft palate only. None of the 39 subjects demonstrated hearing impairment that required a hearing aid. One subject had been classified previously as being educably mentally retarded and received special education.

Information about the distribution of films by age of subject, period of time over which films were available, and number of films available is presented in Tables 1 and 2. Those data indicate that on average, the subjects were nearly 6 years old when the first films were taken, were nearly 14 when the last film was taken, were studied over an 8-year period, and were studied by seven films during that 8-year period. The data indicate also that

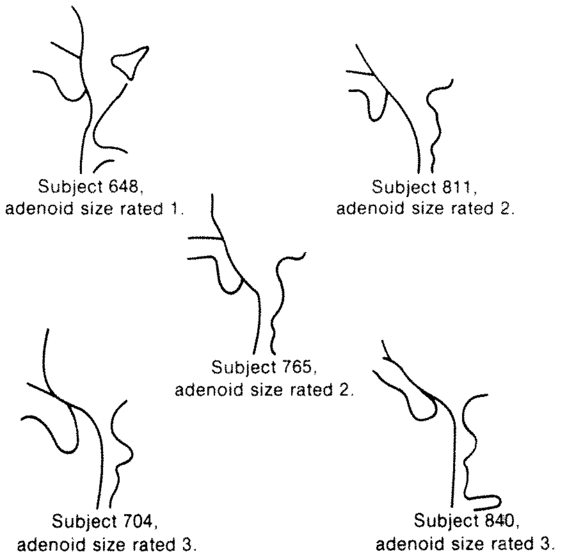
Subject 648, adenoid size rated 1.
Subject 811, adenoid size rated 2.
Subject 765, adenoid size rated 2.
Subject 704, adenoid size rated 3.
Subject 840, adenoid size rated 3.

Fig 1. Some examples of ratings of adenoid size.

films were available at age 17 for only three subjects, and so data for that age level are not considered reliable. Some additional details about subjects and method are reported by Miller.[14]

Procedure. Certain aspects of the procedure were dictated by limitations of the available data (lateral cephalometric films). Obviously, there are methods other than cephalometric films for determining velopharyngeal status that account better for the three-dimensional nature of the mechanism. (For that reason we use here the term velar-pharyngeal to indicate the two-dimensional character of the measure.) On the other hand, our specific interest was in describing the physical relationship between velum and posterior pharyngeal wall/adenoidal pad, as that relationship may change over time, and lateral films yield a fair estimate of that parameter. We used clinical ratings for that purpose; such ratings have been used by a number of investigators and for a variety of general purposes[15,16] and have been demonstrated to be reliable. For the sake of clarity, and to emphasize the limitations of the measure, we refer to it here as velar-pharyngeal contact.

Estimating adenoid size is a difficult problem because of the configuration of the nasopharynx, the differences in configuration among individuals, the lack of easily identifiable landmarks in the nasopharynx, and the difficulties in distinguishing the margins of the adenoid mass from the pharyngeal-nasopharyngeal wall. Several attempts have been made to assess adenoid size by measurement.[2,17-20] However, none of the procedures used seem more reliable or valid for the purposes of this study than a simple clinical judgment of size, and so judgments were used in this study.

Specifically, clinical ratings of adenoid size and midsagittal velar-pharyngeal contact were made from lateral x-ray films during production of /s/. (In some instances, variants of /s/ approaching *sh* were used by smaller children.) Ratings of velar-pharyngeal contact were made prior to this investigation, for another purpose, by two experienced judges.[16] A five-point scale was used for that purpose: 1) good seal, 2) approximately 2 mm of contact, 3) touch contact, 4) velar-pharyngeal space less than 2 mm, and 5) velar-pharyngeal space greater than 2 mm. Interjudge reliability was 0.89.

Ratings of adenoid size were obtained specifically for this study on the basis of the same lateral still x-ray films used for evaluating velar-pharyngeal contact. The ratings were made on a consensus basis by the two senior authors (H.L.M., S.K.M.W.). They first viewed 20 films and established three categories of adenoid size: minimal, rated 1; moderate, rated 2; and large, rated 3 (see Fig 1 for examples). They then practiced on an additional five films. During the judgment process for all films for the 39 subjects, films were selected randomly, and the judges were unaware of which subject or film was being judged. Judgments were made jointly; if the two judges disagreed, they discussed the film until a joint decision was reached. Twenty-four films were evaluated twice to determine consistency of judgments. Reliability of the joint judgments was 0.70 (corrected for guessing). For 23 of the 24 films, the difference between the first and second judgments was no more than one scale point.

Two methods of analysis were used. The first method was a two-way analysis of variance, incorporating subject as a randomized blocking factor, and age class as the factor of clinical interest. These analyses of variance were applied not only to the adenoid size and velar-pharyngeal contact scores discussed above, but also to log and rank transformations of these scores. The clinical inferences obtained from these various analyses were consistent, and so we present only the results on the scores per se.

In the second method of analysis, a random-coefficient growth-curve model was used. This involves a two-stage process. First, after centering the subjects' ages at 11 years old, simple linear regressions of the scores per se were obtained against age for each subject. The two coefficients of these individual regressions (the slope and the intercept, at age = 11) are assumed to be random estimates of the actual regression parameters for the population being sampled in this study. The best estimates of these parameters are pooled estimates obtained by weighting the individual regression estimates by the pooled across-subject variance-covariance matrix for intercept and slope.

RESULTS

Group Trends. Of primary interest were three questions about group trends, as follows.

1. *To what extent did adenoid size change with age, and in what direction was the observed change?*

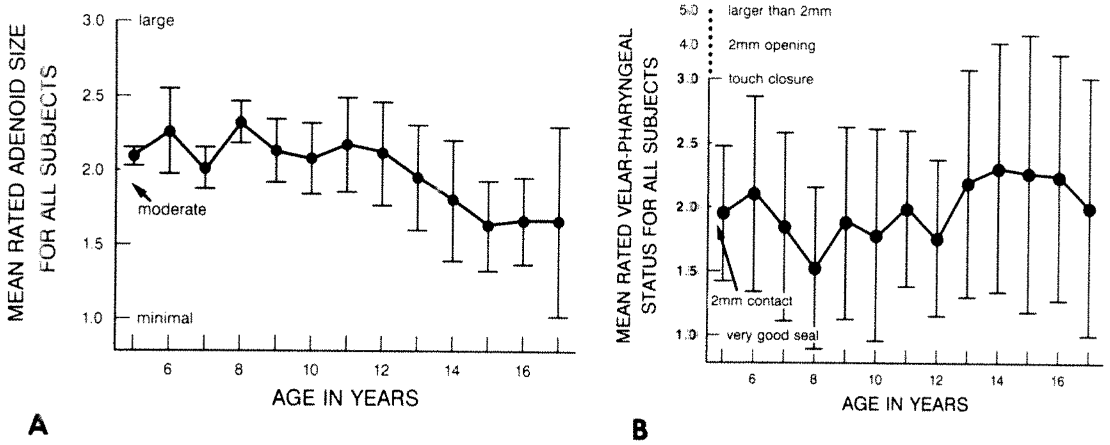

Fig 2. Mean ratings and SDs for A) adenoid size and B) velar-pharyngeal relationships at ages 5 to 17. For ages 5 to 16, films were available from minimum of 11 subjects (at age 15) to maximum of 34 (at age 6) of 39 subjects; films for only three subjects were available for age 17, and so those data are not considered reliable.

Data about adenoid size (mean rating and SD), according to age in years, are shown in Fig 2A. The data show a rather obvious decrease in size over time, although the extent of the decrease is relatively small. Indeed, results of the analysis of variance indicate statistically significant mean differences among the ages. Multiple comparisons (Tukey's Studentized range) indicate that ages 6 and 8 each differ from ages 14 through 16, confirming the trend shown in Fig 2A.

Variations over time in the value of adenoid size also were evaluated by the random-coefficients growth-curve model.[21] In this model, the variation in slope against age in intercept (predicted value at age 11) among these subjects is assumed to be random, given that the subjects form a random sample from a single population being described (Fig 2B). As shown in Table 2, there was a statistically significant negative trend in adenoid size over age, indicating that as expected, adenoid size decreased with age.

2. *To what extent did the status of velar-pharyngeal contact in midline change with age, and in what direction was the observed change?*

Data about velar-pharyngeal contact (mean rating and SD) according to age in years are shown in Fig 2B. Presented in this fashion, the data show maintenance, generally, of a 2-mm contact over time, but with variability within the age period under study. In this instance the analysis of variance indicates no statistically significant differences among the ages.

Variations in velar-pharyngeal contact over time (Fig 2B) also were evaluated by the random-coefficients growth-curve model as described above for adenoid size. As shown in Table 3, the findings indicate no change in velar-pharyngeal contact with increase in age.

3. *To what extent is there covariance between adenoid size and velar-pharyngeal contact?*

Linear and quadratic regression equations of adenoid size on velar-pharyngeal contact were obtained, first based on all 292 ratings, then based on average values for subjects. The standardized R^2 values indicated that in no case was more than 3% of the variation in adenoid size associated with (or related to) variation in velar-pharyngeal contact. The quadratic regressions showed essentially the same relationships between the two variables as did the linear regressions. Additional transformations were used also, and with the same findings. The answer to the question about covariance between adenoid size and velar-pharyngeal contact must be negative.

Findings for Individual Subjects. The data were inspected further to determine whether any of the subjects showed clear evidence of impaired velar-pharyngeal contact with adenoidal atrophy on an individual basis, to the contrary of the group trend.

Three of the 39 subjects showed such evidence; that is, the films indicated loss of velar-pharyngeal midline contact accompanying decrease in adenoid size during the period of study. In one of the three, the velar-pharyngeal dysfunction was diagnosed at age 13; in the other two, the diagnosis was made at ages 15 and 16. Two of the three (including the 13-year-old) showed marked dysfunction and had pharyngeal flap surgery. The third had mild nasalization, and she and her family decided against surgery; no further action has been taken, to our knowledge.

TABLE 3. POOLED ESTIMATES OF COEFFICIENTS FOR EVALUATING VARIATIONS IN ADENOID SIZE AND VELAR-PHARYNGEAL CONTACT OVER AGE

Coefficient	*Estimate + SEM*	t *(38 df)*	*Probability*
Adenoid size			
Intercept (age = 11)	2.0 + 0.03	68.95	p < .0001
Slope	−0.04 + 0.009	−5.03	p < .0001
Velar-pharyngeal contact			
Intercept (age = 11)	2.0 + 0.06	32.52	p < .0001
Slope	0.03 + 0.018	1.55	p = .13

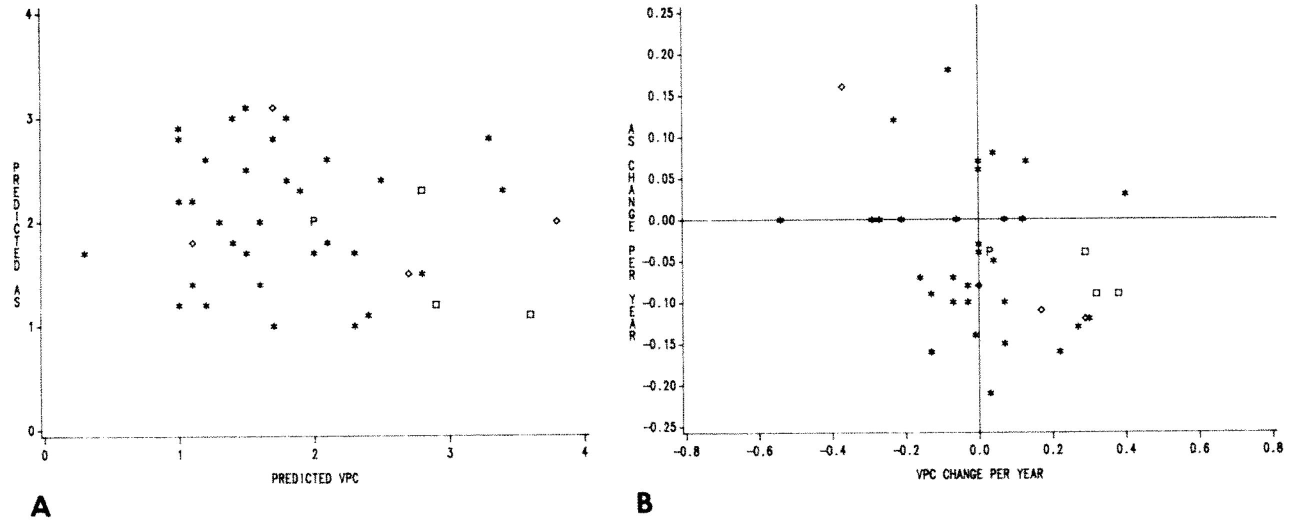

Fig 3. Scattergrams of coefficients obtained from linear regressions of adenoid size (AS) and velar-pharyngeal contact (VPC) scores against age for each subject. P — pooled value obtained from random coefficient growth analysis, squares — those three subjects showing loss of VPC during study, diamonds — those four subjects who showed loss of VPC after completion of study. A) Scores predicted at age 11 for AS, plotted against those for VPC. B) Slopes for AS, plotted against those for VPC.

Information from our data bank about these 39 subjects indicates that an additional four had surgery for velopharyngeal dysfunction after the conclusion of this study. Two of the four had pharyngeal injection (Teflon) for minimal but significant nasalization of speech; the other two had pharyngeal flap surgery for nasalization that was more severe. All four had the surgery at age 15 or 16. Preoperative documentation of adenoid size is available for three of the four. All three show clear velopharyngeal opening during speech by radiographic image before surgery; all three show also small adenoid pads at that examination.

In summary, there was no decrease in velopharyngeal efficiency with adenoidal involution for the group as a whole, when efficiency is assessed by midsagittal contact between the velum and the posterior pharyngeal wall. However, three subjects showed such a change during the period of study, and four more showed such a change after the study was concluded, bringing the total to seven subjects (18%).

However, these seven subjects do not cluster in either of the scattergrams shown in Fig 3, again suggesting that the relationships between these scores over the time period examined are not useful predictors of a need for further surgery. Since all 39 subjects are now 18 years or older, we presume there will be no further changes in status in the group studied.

DISCUSSION

The data reported here indicate rather clearly that the majority of cleft palate subjects who show midline velar-pharyngeal contact against adenoid tissue between the ages of 5 and 7 years are not likely to lose that contact during subsequent years with normal atrophy of the adenoidal pad. A primary limitation to the method used in this study is that the data reflect only structural relationships, and relationships in the midline. As a consequence, they do not reflect functional relationships, or even structural ones not evident in the midsagittal plane. However, to the degree that such midline relationships are an index to velopharyngeal function in general, the findings underscore the likelihood of stability of velar-pharyngeal patterns with normal adenoidal atrophy. Hence, these findings are in general agreement with those reported earlier by Siegel-Sadewitz and Shprintzen.[13]

On the other hand, there are exceptional cases in which the converse seems true. We found three subjects in the group of 39 who lost midline velar-pharyngeal contact with decrease in adenoid size during the course of the study. Clinical information about these three subjects was available from medical and speech pathology records. The records showed that all three developed indications of velopharyngeal dysfunction concurrently with the midsagittal loss of velar-pharyngeal contact. In two of the three, surgical reduction of the velopharyngeal space by pharyngeal flap was subsequently performed. In the third, the extent of dysfunction was mild, and the patient and the family decided against physical management.

As a cross-check, the clinical records for the remaining 36 patients were examined for evidence of developing velopharyngeal dysfunction during the time of study; none showed any such findings. However, these clinical records showed that four of the 36 developed dysfunction after completion of the study and subsequently had pharyngeal flap surgery. Hence, seven of the 39 patients developed velopharyngeal dysfunction during the period of study (between 6 years of age and late adolescence) or later.

The question arises whether these seven subjects are atypical members of the group in rate of change of either adenoid size or velar-pharyngeal status. The scattergram in Fig 3B indicates they are not, although six of the seven are clustered in one quadrant (less change in adenoid size and more change in velar-pharyngeal status than typical of the group). Certainly, they could not be considered outliers on the basis of the available information.

The challenge to the clinician is to be able to identify these patients who are likely to show clinically significant deterioration of velopharyngeal function during adolescence even though function appeared adequate in earlier childhood. Mason and Warren[11] have suggested the usefulness of aerodynamic measures for such a purpose. There may be other measures as well. Two possibilities are physical measurements of palatal length and nasopharyngeal depth and width, which might indicate structural deficiencies of the velopharyngeal mechanism. Additional information about danger signals, particularly from measures readily available to the clinician in general practice, will be very useful. Patients showing such danger signals then could be studied more closely, and they and their families could be better advised about the possibility of developing nasalization of speech. Investigations designed for that purpose should have high priority.

Until such information is available, the main clinical implication of these findings is that cleft palate patients should be evaluated by the speech pathologist on a periodic basis through adolescence, even though they demonstrate normal velopharyngeal function at earlier ages. Alternatively, the family of such a patient can be advised to be alert for any changes in speech resonance during that period and to seek examination by a speech pathologist should they be evident.

There are several design limitations to this study that require comment. One was mentioned earlier in this discussion; it is that both adenoid size and velar-pharyngeal relationships were estimated from a single lateral cephalometric film, which provides information in only two dimensions and in the midline. Such information could be misleading when the adenoidal pad or velopharyngeal opening differ markedly in the sagittal plane from planes lateral to it.

There are indications also that the period of study was not long enough. Four of the 39 subjects apparently developed velopharyngeal dysfunction at ages 15 and 16, when data in this study indicated satisfactory function at the previous evaluations. The period of study for most subjects ended at 14 or 15 years of age; perhaps different findings for the group would have been obtained had the study been extended further into the late teens. The question also remains whether the loss of velar-pharyngeal contact at this "late age" was the result of adenoidal atrophy, since presumably the major effects of normal atrophy would be experienced earlier. Further investigation is needed.

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CORRECTION OF GLOTTIC INSUFFICIENCY BY COLLAGEN INJECTION

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Thirty-nine patients were treated with GAX collagen for vocal fold augmentation. The objective results were evaluated by measurement of the maximum phonation time, the phonatory quotient, vocal frequency analysis, and laryngostroboscopy. These results are as good as those with Zyderm Collagen II (ZCI). Avoidance of useless overcorrection, better resistance to collagenase, and less induced hypersensitivity differentiate GAX from ZCI.

KEY WORDS — collagen, glottic insufficiency, larynx.

INTRODUCTION

After the experimental work by Ford et al[1,2] and ourselves[3] on the canine larynx, injectable collagen seemed to be an attractive alternative to Teflon in laryngeal and vocal rehabilitation. It is a natural constituent of the lamina propria of the vocal fold, and is very well tolerated, allowing host tissues to grow into the implant. Furthermore, it appears to become progressively replaced by host collagen. A form called ZCI (Zyderm Collagen II; Collagen Corp, Palo Alto, Calif) was the first injectable collagen used for clinical work.[4,5] It is a highly purified suspension (65 mg/mL) of bovine dermal collagen in a buffered physiologic saline solution containing 0.3% lidocaine. The results of Ford et al on 54 patients, and ours on 25 patients, have shown that ZCI is well tolerated, is easy to inject, and provides functional results that are at least as good as those achieved with Teflon. The results remain stable for at least 3 years.[6,7]

Results of studies of human laryngeal specimens after collagen injection corroborate the results of animal histologic studies.[8,9] However, ZCI does have some disadvantages. 1) It is not cross-linked, and its sensitivity to fibroblast-secreted collagenase could lead to long-term resorption. 2) The microfibrils consolidate in situ after the injection. 3) Water — a volume equivalent of at least 60% of the injected volume of collagen — is eliminated, requiring overinjection. Three percent to 4% of patients injected with ZCI are hypersensitive to it.

A new collagen preparation, GAX collagen (Phonagel; Collagen Corp), became available in 1986, and we began using it in May 1986 to solve the problems posed by ZCI. This new product contains a 0.0075% glutaraldehyde cross-linked collagen that is practically collagenase-insensitive. It is not consolidated in situ, so no water is eliminated and the injected volume remains stable. Less than 1% of the population is hypersensitive to GAX.[10,11]

MATERIALS AND METHODS

Since May 1986, we have used GAX collagen to treat 53 patients, 39 of whom needed a vocal fold augmentation. These 39 patients were divided into four treatment groups: unilateral vocal fold paralysis (n = 29), cricoarytenoid ankylosis (n = 2), post–laryngeal surgery (n = 5), and hypotonia or presbyphonia (n = 3) (Tables 1-3). Twenty patients were injected for dysphonia. Nine patients (eight with vocal folds paralyzed in an intermediate position, and one with cricoarytenoid ankylosis) were treated for aspiration problems and dysphonia.

The 14 remaining patients were not treated for vocal fold augmentation and form the subject of a separate report. In eight of these patients we injected collagen into the arytenoids and the aryepiglottic folds to treat aspiration problems that occurred after reconstructive laryngeal surgery. In

TABLE 1. DEMOGRAPHIC DATA

Treatment Group	*No. of Patients*	*Male/ Female Ratio*	*Age (yr)*		*Follow-Up (mo)*	
			Mean	*Range*	*Mean*	*Range*
Unilateral vocal fold paralysis	29	20:9	54	14-74	13	1-33
Cricoarytenoid ankylosis	2	1:1	39.5	26-53	14	3-25
Post–laryngeal surgery	5	3:2	60.4	53-72	15	2-20
Hypotonia or presbyphonia	3	2:1	45.6	24-74	12	4-24
All groups	39	26:13	53.4	14-74	13	1-33

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TABLE 2. TREATMENT GROUPS

	No. of Patients	*Left Vocal Fold*	*Right Vocal Fold*
Unilateral vocal fold paralysis	29	23	6
Intermediate position	22	18	4
Paramedian position	7	5	2
Cricoarytenoid ankylosis	2	1	1
Post–laryngeal surgery	5		
Vocal fold defect after microsurgery	1		
Endoscopic double cordectomy	1		
Hemilaryngectomy	2		
Reconstructive laryngectomy	1		
Hypotonia or presbyphonia	3		

four patients we injected collagen into the posterior pharyngeal wall, facing the velum, to treat velopharyngeal insufficiency, and in two we injected collagen to correct an enlarged tracheoesophageal fistula for a vocal prosthesis.

If the cause of vocal fold immobility is unknown, vocal fold electromyography is carried out to determine the site of nerve injury. If a lesion of the inferior laryngeal nerve does not appear to be total, we delay any surgical therapy for 6 months. In addition to voice recording, objective estimation before and after treatment includes maximum phonation time, phonatory quotient, and voice frequency analysis with the Bruel & Kjaer 2033 high-resolution frequency analyzer, which permits the investigation of fundamental frequency and harmonics.[12] The patient's collagen tolerance is tested with a 0.1-cm^3 subcutaneous injection into the forearm. The injection site normally is observed for 1 month for signs of intolerance such as redness or induration. However, this delay is shortened to 10 days in the case of severe aspiration problems. To date, this reaction has not occurred in any of our patients. Speech therapy should be started as soon as possible and pursued after the injection. When folds are initially paralyzed in a paramedian position, speech therapy alone very often proves adequate. In such cases, the indication for injection is an excessive tendency to vocal fatigue or the patient's refusal of speech therapy.

TABLE 3. CAUSES OF VOCAL FOLD PARALYSIS

Iatrogenic causes	13
Thoracic surgery	5
Thyroid surgery	4
Carotid surgery	1
Extended radical neck dissection	1
Pneumogastric nerve chemodectoma surgery	1
Acoustic neuroma surgery	1
Neuritis	7
Bronchopulmonary neoplasm	6
Pulmonary and pleural fibrosis	2
Post-tuberculosis	1
Post-mycoplasma	1
Esophageal neoplasm	1

The injection usually is performed under microscopic control during suspension laryngoscopy and general anesthesia. The patient is ventilated through a No. 6 tracheal tube or with high-frequency jet ventilation. Should general anesthesia be contraindicated, the injection then is performed by means of the technique of Ford and Bless[4] of indirect laryngoscopy with local anesthesia. Postoperative care is very simple. The patient leaves the hospital after 24 to 48 hours. Broad-spectrum antibiotics are given for 6 to 8 days. We then examine the patient monthly by indirect laryngoscopy for the next 3 months, and once every 3 months thereafter for 1 year. The phonatory measurements are carried out during each checkup.

Technique for Injection. Since 1986, we have been using the injection tube designed by Collagen Corp (Fig 1). This tube offers many advantages. It is light and easy to handle, and the GAX collagen syringe can be simply inserted into the barrel. Its lumen is filled with only 0.13 cm^3 of collagen, which ensures minimal loss. A sterile, disposable 27-gauge needle screws onto the tip. Hence, the exact quantity needed can be injected atraumatically into the tissues. To ensure a good view of the injec-

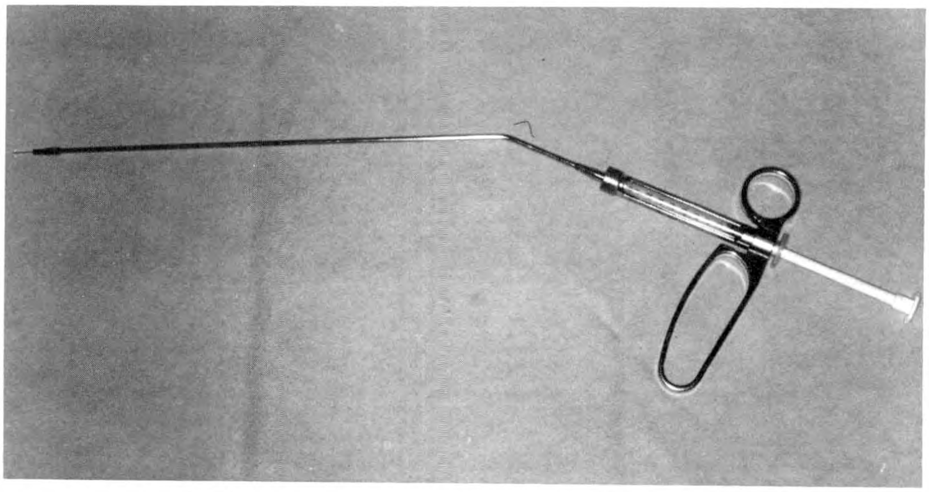

Fig 1. GAX collagen injecting device. Collagen syringe is inserted into barrel, and sterile disposable 27-gauge needle is fixed onto tip.

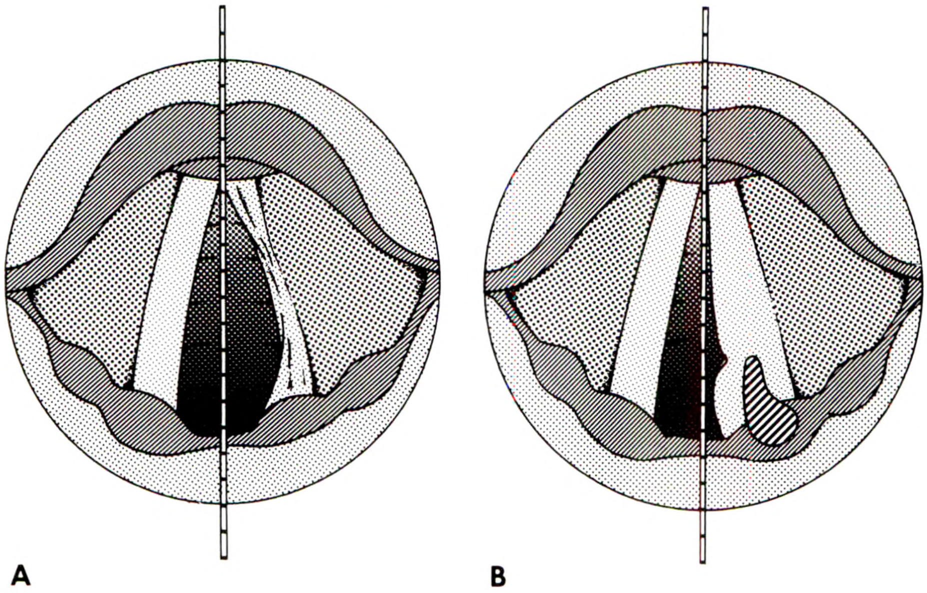

Fig 2. Aspect of intermediate vocal fold paralysis. Vocal fold is atrophic. Volume augmentation and displacement of free edge of vocal fold to laryngeal medial line can be seen. A) Before collagen injection. B) After correct collagen injection.

tion, the needle can be bent without risk of breaking.

We agree with Ford and Bless[6] about the depth of injection into the vocal fold. Puncture is performed through the superior surface of the vocal fold into the deep part of the lamina propria or vocal ligament. Injection must be slow. If the collagen is injected into the correct place, the volume augmentation and displacement of the free edge of the vocal fold to the laryngeal medial line can be seen (Fig 2). The vocal fold must keep its usual color. If the injection is too superficial, a whitening of the vocal fold will be readily apparent around the needle at the start of the injection. The implant also tends to loculate and distend the superficial lamina propria or Reinke's space. A too-superficial deposit can be dispersed readily, for instance, with the edge of a small, unconnected laryngeal suction device. The needle then must be driven slightly deeper before further injection is carried out. If the collagen is injected too superficially, into Reinke's space, the wave motion of the mucosa on the vocal ligament will definitively disappear. The voice may be louder, but the timbre will remain poor. On the other hand, if the injection is too deep and is performed into the vocal muscle, the volume augmentation of the vocal fold and its displacement to the medial line will not be obtained. This, of course, is because of the thyroarytenoid muscle volume and the dispersibility of the collagen (Fig 3A). In addition to the fact that a huge quantity of collagen is required, injection into the muscle could result in rapid resorption of the implant.

Collagen injection is carried out into three major points to obtain a good medialization of the vocal fold from the front to the rear (Fig 3B). The first injection point is just in front of the vocal apophysis in the superior surface of the vocal fold. Injection at this point allows the collagen to diffuse from the apophysis to the anterior commissure. However, a

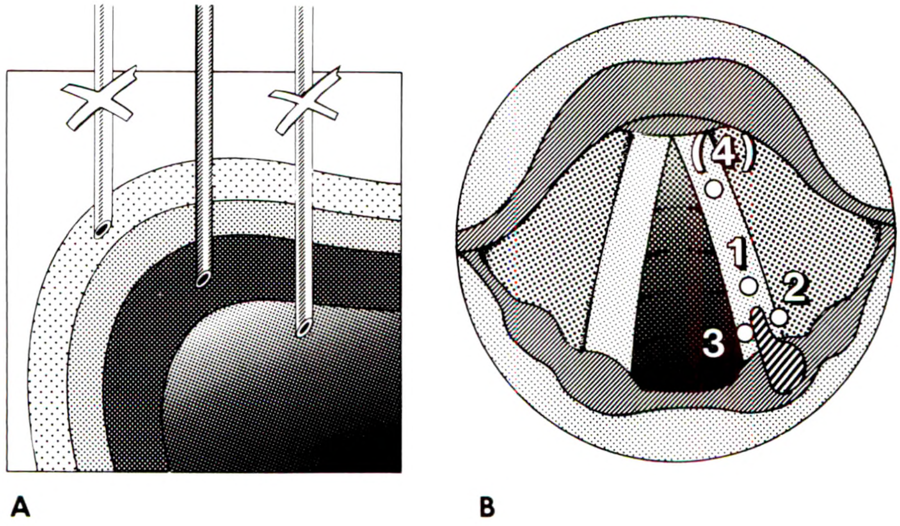

Fig 3. Correct points of injection. A) Correct insertion of needle into deep part of lamina propria (vocal ligament). Insertion into superficial part (Reinke's space) or into vocal muscle must be avoided. B) Major injection points to obtain good medialization of vocal fold. 1 — in front of vocal apophysis, 2 — lateral to apophysis. 3 — medial to apophysis, 4 — anterior.

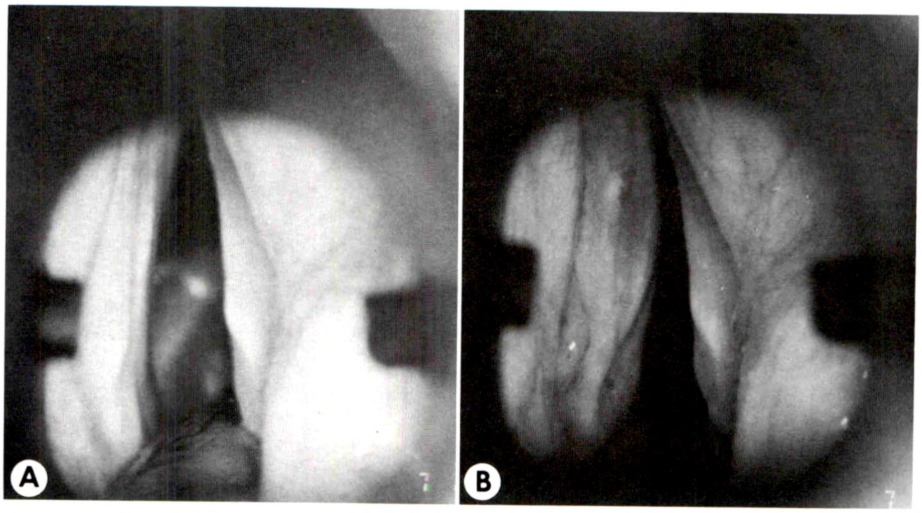

Fig 4. Endoscopic views of left vocal fold paralysis. A) Before collagen injection. B) After collagen injection.

good medialization of the vocal apophysis itself must be achieved, and that is why the injection is completed by a second puncture lateral to the vocal apophysis. Although more difficult, it is also possible to inject a small quantity (0.1 to 0.2 cm^3) through a third puncture medial to the vocal apophysis. Using the two posterior punctures, which we consider very important, we can avoid a posterior glottic gap during phonation. If necessary, a fourth puncture can be made anteriorly to achieve good uniform medialization.

The situation is, of course, completely different after partial or reconstructive laryngeal surgery. Then the normal vocal fold structure has disappeared completely, and there remains only a fibrous tissue. It is very important to inject slowly and to look for a plane within which the collagen can spread easily. If injection is too fast, or into too fibrous an area, a reflux of collagen results. A pad with the rough shape of a vocal fold is progressively constituted in this way. If necessary, injection can be repeated several times. The volume of collagen needed varies from one indication to another. An intermediate paralysis usually requires 1 to 1.5 cm^3. A paramedian paralysis requires only 0.2 to 0.5 cm^3. On the other hand, 2 to 6 cm^3 can be used for a postoperative case because of the volume necessary for adequate displacement and some loss due to reflux. Injecting only the necessary volume is of great importance, because GAX collagen remains stable; this contrasts with the overinjection required with use of ZCI collagen (Fig 4).

TABLE 4. SUBJECTIVE RESULTS (TO OCTOBER 1988)

Treatment Groups	*Dysphonia*		*Aspiration Problems*	
Unilateral vocal fold paralysis (n = 29)	Very good	19/29	Very good	2/7
	Good	10/29	Good	3/7
			Fairly good	2/7
Cricoarytenoid ankylosis (n = 2)	Good	1/2	Good	1/1
	Fairly good	1/2		
Post-laryngeal surgery (n = 5)	Very good	1/5		
	Good	1/5		
	Fairly good	1/5		
	Poor	2/5		
Hypotonia/presbyphonia (n = 3)	Good	2/3		
	Fairly good	1/3		

Very good — practically normal, good — moderate problem occasionally, fairly good — moderate problem frequently, poor — moderate or severe problem frequently or constantly.

RESULTS

To date, subjectively as well as objectively, the results are very favorable for the 39 patients treated. The immediate follow-up was very simple; there was no damage to the vocal folds resulting from injection of collagen. No patient has been found to have laryngeal edema requiring corticosteroids, prolonged intubation, or tracheotomy. Since we began performing collagen injections, with either ZCI or GAX, only one of 78 patients has been rejected because of a cutaneous hypersensibility to the tolerance skin test.

The results differed according to the injection indication (Table 4). The best vocal results were achieved when the vocal fold structure was undamaged, as in laryngeal nerve paralysis. In these cases, not only did the voice intensity increase while vocal fatigue and breathiness decreased, but the timbre and clarity of the voice also improved. Singing, however, remained difficult. On the other hand, in those postoperative cases in which the shape of the vocal fold was reconstructed, the voice was louder and vocal fatigue and breathiness decreased, but vocal timbre remained poor. Patients suffering from difficulties in swallowing also have found that these have been lessened considerably.

The objective results, both quantitative and qualitative, confirmed the subjective improvements. The control indirect laryngostroboscopy showed a good glottic closure during phonation and a wave

TABLE 5. OBJECTIVE RESULTS

Treatment Groups	*Maximum Phonation Time (s)*				*Phonatory Quotient (mL/s)*			
	Pretherapy		*Posttherapy*		*Pretherapy*		*Posttherapy*	
	Mean	*Range*	*Mean*	*Range*	*Mean*	*Range*	*Mean*	*Range*
Unilateral vocal fold paralysis (n = 29)	7.4	3 -14.5	14.6	7.7-26	668	163-1,661	274	120 -534
Cricoarytenoid ankylosis (n = 2)	9	9 -10	13	10 -16	362	252- 472	222.5	220 -225
Post–laryngeal surgery (n = 5)	15.5	4.2-36.5	21.1	7 -43	603.6	194- 877	340.2	123.6-569
Hypotonia/presbyphonia (n = 3)	6.7	5.3- 8	10.5	8.4-13	288.3	250- 340	225	180 -270

Postoperative data are calculated from most recent examination, time of which varies from subject to subject.

motion of the mucosa on the vocal ligament symmetric with that of the mobile vocal fold from the third postoperative week. The quantitative phonatory measurements (Table 5 and Fig 5) showed a clear improvement of voice efficiency from the first days after the operation. Nevertheless, a decline in results was noted around the sixth month in the unilateral vocal fold paralysis group. This decline occurred because some subjects in this group developed diminished pulmonary function due to advanced stages of bronchopulmonary cancer. After their death, satisfactory stability of the group values was resumed. We used vocal frequency analysis for objective qualitative measurements of voice (Fig 6). This analysis was of greatest importance when the vocal fold structure was respected, as in the paralysis cases. On the plates representing intensity as a function of frequency, the peaks corresponding to fundamental frequency and harmonics were improved, their summits were no longer crushed, the frequency range filled by each of the peaks was decreased, and parasite noises and hooks disappeared. Missing harmonics were found again. On the plates showing intensity as a function of time, a clear increase and maintenance of the intensity during emission were noted. In the postoperative group, increased intensity was found again, but enrichment in harmonics was not very marked, and the fundamental frequency peak remained widened, with a crushed top and hooks.

The results may improve with time and speech therapy; they remain stable to date. The mean follow-up was 13 months (range, 1 to 33 months; Table 1).

DISCUSSION

The functional results achieved with GAX collagen are equivalent to those with ZCI.[10,11] The fact that the injected volume remains stable is a major security element. There is no longer the risk of creating a very narrow glottic lumen during the first 2 or 3 days with a hypercompensatory injection, as could happen with ZCI. However, the need for precisely placing the injection is greater for GAX than for ZCI. With ZCI, the injection could be done at all levels of the lamina propria.[5,7] After the resorption of the saline solution, which represents 50% to 60% of the volume, the ballooned vocal fold straightened out. The mucosa was again able to undulate on the vocal ligament. By contrast, a precise amount of GAX must be injected into the deep part of the lamina propria. Otherwise, there is a risk of permanent ballooning and stiffness with too superficial a deposit of the GAX collagen, resulting in loss of the mucosal wave. We therefore prefer to use direct laryngoscopy, general anesthesia, and microscopic control, which allow us to be very precise. With local anesthesia and indirect laryngoscopy, any attempts by the patient to cough or swallow during the procedure may cause the injection to be done in the wrong place or may cause an incorrect

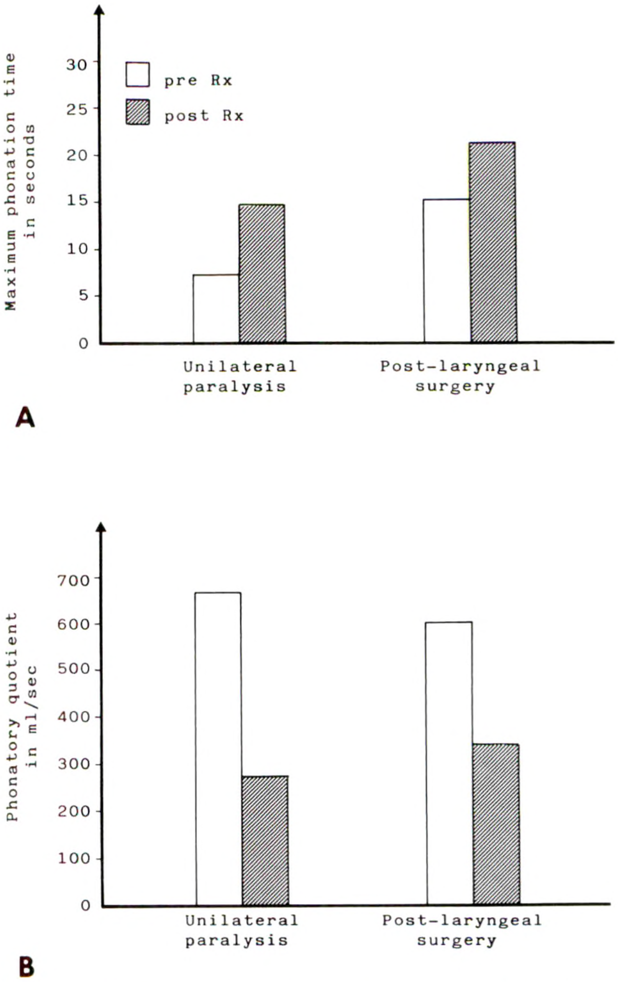

Fig 5. Histograms showing average improvement in A) maximum phonation time and B) phonatory quotient for unilateral vocal fold paralysis and post-laryngeal surgery groups.

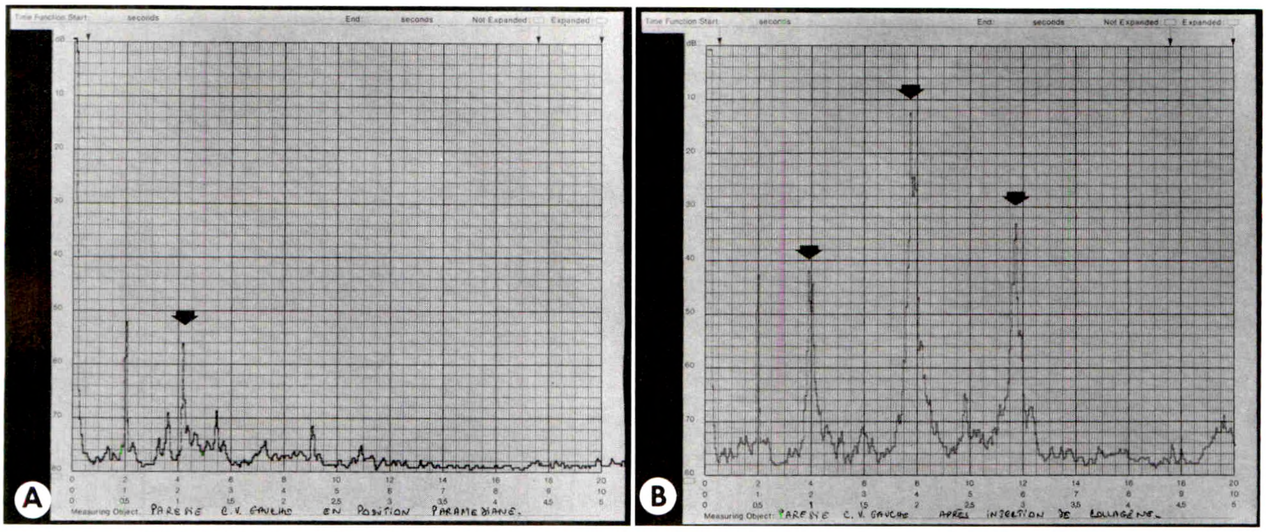

Fig 6. Voice frequency analysis of man with vocal fold paralysis in intermediate position. Intensity (linear scale in millivolts) as function of frequency (0 to 1,000 Hz). A) Before collagen injection. Only fundamental frequency is seen at 100 Hz (arrow). Harmonics have completely disappeared. Intensity of fundamental frequency is weak. B) After collagen injection. Intensity of fundamental frequency is improved, and first harmonics are found again (arrows).

amount of collagen to be injected. Such maneuvers as smoothing the treated vocal fold to produce a better distribution of the collagen also are difficult to perform with local anesthesia. Of course, our technique has the disadvantages of general anesthesia and the lack of perioperative voice control. We use general anesthesia only after a careful preoperative assessment. If there is any contraindication, the injection is made with local anesthesia and indirect laryngoscopy according to Ford and Bless.[6] As for the lack of perioperative voice control, it is our belief that the vocal results will be satisfactory when correct medialization of the injected vocal fold is achieved; this means that the free edge of the vocal fold reaches the laryngeal median line.

Fewer than 1% of subjects are hypersensitive to GAX collagen, whereas 3% to 4% are hypersensitive to ZCI. This series[7] plus those reported by Ford et al[4,6,10] represent over 150 patients injected with collagen without a substantial hypersensitivity reaction; Ford et al[6,10] reported a single incident of postinjection erythema of the vocal fold. The risk of aspiration seemed to us greater than the likelihood of hypersensitivity, so we elected to shorten the tolerance test time to 10 days in selected patients with severe swallowing difficulties.

GAX collagen, which is cross-linked, is much less sensitive to fibroblast-secreted collagenase than is ZCI. Consequently, more stable results can be achieved with GAX than with ZCI. It is noteworthy that the ZCI results extend back more than 3 years.[13]

The issue of longevity is not settled at this time. The persistence of the results in the larynx seems superior to that obtained with the correction of facial wrinkles and depressed scars. This may be explained in part by the dispersion of the collagen resulting from movements of the facial muscles. Collagen fibers, like elastic fibers, can break under the influence of the mimetic muscles and cause the reappearance of wrinkles.

Because we do not know if the results achieved with GAX collagen will persist longer than 3 years, there remains an argument in favor of Teflon. Although Teflon has been very useful for vocal rehabilitation since its introduction by Arnold[14] in 1962 and its utilization by Dedo[15] in 1973, the risks of local inflammatory reactions are well known.[16-20] Moreover, the viscosity of injectable Teflon, the size of the injection device, and the needle diameter do not allow the precise injection afforded by the use of collagen.

The injection of bronchopulmonary cancer patients can be criticized because of their poor prognosis. However, in our opinion, achieving laryngeal rehabilitation is very important for the quality of life of these patients. Dysphonia is one of the main symptoms of the disease; it can handicap family life as well as social and professional communication. Moreover, correct glottic closure ensures an effective cough and diminishes possible aspiration problems resulting from the glottic immobility.

CONCLUSION

Functional results achieved with GAX collagen are as good as those obtained with ZCI, provided that the injection is made strictly into the vocal ligament. Injection under microscopic control during suspension laryngoscopy is, in our opinion, the most reliable technique to ensure the spread of collagen along the whole vocal fold. Made to offer better resistance to collagenase and to induce less hypersensitivity, GAX collagen is also more effective than ZCI because overcorrection is no longer necessary. Its low viscosity allows injection through a 27-gauge needle and injection into places that are difficult, if not impossible, to inject with Teflon, such as medial to the vocal apophysis. It is well tolerated by host tissues, and therefore superior to Teflon, which can induce inflammatory reactions. How long GAX collagen will persist in rehabilitated vocal cords and larynges is not known. On the basis of the results achieved in patients injected over 3 years ago with ZCI, is seems likely that the correction achieved with GAX will persist.

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OTOLARYNGOLOGIC MANAGEMENT OF POSTTRANSPLANT LYMPHOPROLIFERATIVE DISEASE IN CHILDREN

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Twelve of 14 children (86%) given a pathologic diagnosis of posttransplantation lymphoproliferative disease (PTLD) at the Children's Hospital of Pittsburgh presented with head and neck symptoms, and are included in this retrospective analysis. Upper airway obstruction was the most common symptom, evident in nine children (75%). Ten children (83%) had febrile illnesses with dysphagia, odynophagia, and evidence of hypertrophy of components of Waldeyer's ring. Associated findings included cervical adenopathy, sinusitis, and otitis media. The two remaining children had an intratracheal and paratracheal mass, respectively. Excision of obstructing lymphoid tissue with proper handling of the specimen is advocated for diagnosis and relief of airway obstruction. Systemic therapy is necessary for treatment of PTLD and includes reduction of immunosuppression. Erythromycin causes elevation in cyclosporine levels and should be avoided in patients taking this drug.

KEY WORDS — cyclosporine, Epstein-Barr virus, erythromycin, lymphoproliferation, stridor, transplant.

INTRODUCTION

Posttransplantation lymphoproliferative disease (PTLD) is a complication of the immunosuppressive drug therapy that transplant recipients require to avoid rejection of their graft organs. Development of the disease is associated with Epstein-Barr virus (EBV) infection; presentation is commonly with otolaryngologic symptoms. Recognition of this clinical entity has become increasingly important for the otolaryngologist–head and neck surgeon as the transplant population increases. This report summarizes a retrospective analysis of the experience at the Children's Hospital of Pittsburgh with children having otolaryngologic manifestations of PTLD. Recommendations for management are made.

METHODS

We reviewed all cases of PTLD recorded by the Department of Pathology at the Children's Hospital of Pittsburgh. Patients were included in this study if chart review documented otolaryngologic findings on presentation. Inpatient charts were obtained from the Medical Records Department; further follow-up data were gathered from the Organ-Transplantation Department's records. Pathology slides were reviewed for each patient.

Although the diagnosis of PTLD is made by biopsy, the pathologic appearance is variable and reflects a spectrum of proliferation of B-lymphocytes. Grossly, the lesions may appear as solid tumors, as parenchymal infiltrates, or as enlargement of lymphoid tissues. Microscopically, lesions often appear reactive and show maturation of B-lymphocytes in a polymorphic pattern. This polymorphic appearance may be similar to the lymphoproliferation of infectious mononucleosis. Underlying architecture may be retained or destroyed by lymphoid infiltrates, and necrosis is often extensive. In contradistinction, other lesions have a monomorphic appearance and resemble non-Hodgkin's lymphoma. Immunocytochemical and recombinant DNA techniques may be used to identify specific subpopulations of proliferating lymphocytes. Proliferation of B cells may be monoclonal or polyclonal in PTLD, or there may be a monoclonal component in a background of polyclonal proliferation. Clonality does not necessarily reflect the clinical aggressiveness of the lesion.[1]

The classification of histopathologic subsets, eg, lymphoma versus B cell hyperplasia, in the spectrum of PTLD is controversial at this time.[2] The language used for pathologic diagnoses and histologic descriptions in this report is taken from the formal pathology reports at the Children's Hospital of Pittsburgh.

As there is an association between EBV infection and the development of PTLD, serologic evidence of primary or reactivation EBV infection was compiled.[2] In some cases tissue was stained for the Epstein-Barr nuclear antigen (EBNA) or recombinant DNA techniques were used to document the presence of EBV DNA in lymphoid tissue.

RESULTS

Fourteen children received pathologic diagnoses of PTLD between December 1984 and May 1988 at the Children's Hospital of Pittsburgh. Two patients had gastrointestinal complaints without otolaryngologic symptoms. Twelve cases (86%) involved head and neck manifestations and were included in

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CHILDREN WITH POSTTRANSPLANT LYMPHOPROLIFERATIVE DISEASE AND OTOLARYNGOLOGIC MANIFESTATIONS

Case	*Sex*	*Age (yr)*	*Time Since Transplant*	*Symptoms and Signs at Presentation*	*Cervical Nodes*	*Non-Head and Neck Nodes*	*Epstein-Barr Virus Infection*	*Surgical Procedures*	*Outcome*
1	F	2	2 mo	Fever, exudative tonsillitis	+	+	+	Tonsillectomy, adenoidectomy, tracheotomy	Discharged, no recurrence
2	M	2	1 yr 1 mo	Recurrent otitis media, nasal obstruction, nasal mass	–	–	–	Adenoidectomy	Discharged, no recurrence
3	F	10	2 yr 1 mo	Upper airway obstruction, Waldeyer's ring hypertrophy, abdominal pain	+	+	+	Adenoidectomy	Did well, then developed recurrent fevers
			3 yr 1 mo	Persistent fever, renal failure	?	+	+	Axillary node biopsy	Dead of non-Hodgkin's lymphoma (large cell)
4	F	5	2 yr 2 mo	Fever, adenotonsillitis, sinusitis, upper airway obstruction	+	–	+	Tonsillectomy, adenoidectomy	Discharged, no recurrence
5	M	4	11 mo	Fever, abdominal pain, nasal obstruction, new-onset snoring	+	+	+	Node biopsy	Discharged, no recurrence
6	M	8	7 mo	Fever, adenotonsillitis	+	+	+	Tonsillectomy, adenoidectomy, node biopsy	Discharged, no recurrence
7	M	12	1 yr 1 mo	Fever, adenotonsillitis	+	–	+	Adenoidectomy	Discharged, no recurrence
8	M	3	2 mo	Fever, hoarseness, adenoiditis	–	–	–	Adenoidectomy	Discharged, no recurrence
9	M	15	6 mo	Tonsillar hypertrophy	–	–	?	Unilateral tonsillectomy	Discharged, no recurrence
10	F	15	13 yr	Rejection treated with cyclosporine A, fever, adenotonsillitis, upper airway obstruction	+	+	+	Unilateral tonsillectomy, node biopsy	Death due to posttonsillectomy bleeding, autopsy showed disseminated PTLD
11	F	10	5 yr 10 mo	Stridor (tracheal mass)	–	–	+	Multiple endoscopies	Death after chemotherapy and irradiation for PTLD
12	F	11	2 yr 10 mo	Cough, paratracheal mass	–	–	+	Biopsy of paratracheal mass	Follow-up <2 mo

PTLD — posttransplant lymphoproliferative disease.

this analysis. There were six girls and six boys. Patients' ages at presentation ranged from 2 years to 15 years. Ten patients had received liver transplants and two patients had received kidney transplants. The interval from transplantation to diagnosis of PTLD ranged from 2 months to 13 years. In 10 of the 12 children (83%) cyclosporine A (CsA) was the principal immunosuppressive agent used after transplantation. In the CsA-treated group, the duration of therapy prior to diagnosis with PTLD ranged from 2 months to 5 years, with an average treatment of 18 months prior to the diagnosis of PTLD.

The symptoms at presentation were consistent with a severe upper respiratory tract infection in most children. Ten patients had febrile illnesses with dysphagia, odynophagia, nasal obstruction, or "noisy" breathing. These patients all had evidence of hypertrophy of the tissues in Waldeyer's ring on physical examination. The tonsils and adenoids on physical examination and at operation were usually described as friable with shaggy necrotic exudate.

Significant upper airway obstruction requiring close monitoring or establishment of an artificial airway occurred in nine patients. Adenotonsillar hypertrophy was the source of obstruction for eight patients. These patients experienced new-onset snoring, sleep apnea, and nasal obstruction. One patient had a tracheal mass that caused biphasic stridor.

Significant cervical adenopathy was noted in 7 of the 12 patients. Although 5 children also had inguinal or axillary adenopathy, no patient in this report had inguinal or axillary adenopathy without cervical adenopathy.

Other associated disorders included otitis media and sinusitis. Otitis media was diagnosed by pneumatic otoscopy in five children, all with adenotonsillar hypertrophy. Six of seven children who had sinus radiographs were given a radiographic diagnosis of sinusitis. The only child with negative findings on sinus films had a tracheal mass without adenotonsillar hypertrophy.

Clinical characteristics of this series are summarized in the Table. Epstein-Barr virus infection was identified by serology, by the presence of EBNA in tumor cells, or by incorporation of viral DNA into tumor cells. Results were available in 11 patients. In 9 patients the results were consistent with primary or reactivation EBV infection.

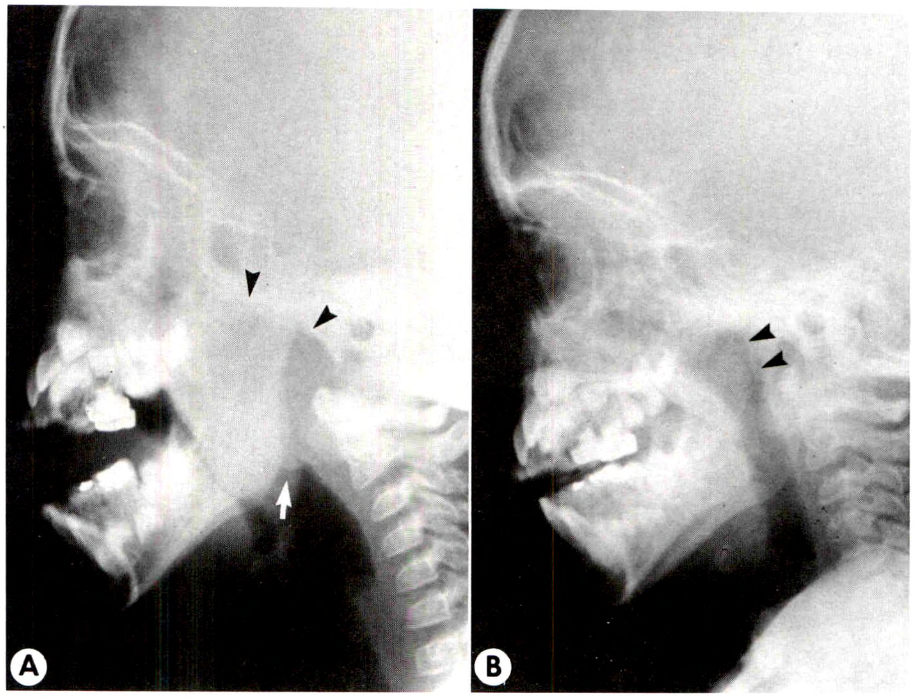

Fig 1. (Case 4) A) Before tonsillectomy and adenoidectomy. Black arrowheads — obstructive nasopharyngeal mass, white arrow — enlarged palatine tonsils. B) After tonsillectomy and adenoidectomy. Oropharynx is now clear. Arrowheads — patent nasopharynx in postoperative examination.

All 12 children underwent operations for tissue diagnosis of PTLD (see Table).

Three deaths occurred in this series. Two deaths were from aggressive PTLD with associated sepsis, and one death occurred as a complication of tonsillectomy in a child with disseminated PTLD.

The clinical spectrum of PTLD ranges from an infectious mononucleosis-like syndrome, frequently of exaggerated severity with respiratory compromise, to widely disseminated invasive disease. Four cases illustrate the otolaryngologic presentations of PTLD.

CASE REPORTS

Case 4. A 5-year-old girl (2 years following liver transplant) was admitted for intravenous hydration after a 2-week history of fever, sinusitis, and pharyngitis treated with oral antibiotics. A monospot test was positive. Physical examination revealed otitis media, exudative tonsillitis with 4+ tonsils, purulent-appearing rhinorrhea, and marked nasal obstruction (Fig 1). Maintenance medications included prednisone and CsA.

A nasopharyngeal tube was inserted after she was noted to have 5-second apneic periods despite respiratory efforts. Symptoms of upper airway obstruction were relieved by adenotonsillectomy. Histologic examination of the tonsils and adenoids showed effacement of the normal architecture by sheets of polymorphic lymphoid cells with numerous mitoses and prominent areas of necrosis. Reed-Sternberg–like cells were described. Immunohistochemical findings were consistent with polyclonal lymphoproliferation. Epstein-Barr virus DNA was identified in the specimen.

The patient continues to do well 2 years following diagnosis of PTLD and subsequent diminution of CsA and steroids.

Case 2. A 2-year-old boy (1 year following liver transplant) was treated with multiple antibiotics including erythromycin for recurrent episodes of otitis media and coryza. Adenoidectomy and bilateral myringotomy and tubes were recommended, and a necrotic-appearing obstructive nasopharyngeal mass was noted at operation. Microscopic examination showed effacement of normal adenoidal architecture by a population of large lymphoid cells with prominent nucleoli and variable amounts of cytoplasm, resembling Reed-Sternberg cells. Admixed were plasma cells, lymphocytes, and macrophages. Large areas of necrosis with bacterial and fungal overgrowth were described. Serologic findings were consistent with EBV infection.

This patient's markedly elevated CsA level (2,417 ng/mL) despite an unchanged dosage schedule reflects the effect of erythromycin administration on CsA excretion. He did well after diminution of the CsA dose.

Case 10. A 15-year-old girl (13 years following liver transplant) developed a rapidly progressive febrile illness with upper airway obstruction, dysphagia, Waldeyer's ring hypertrophy, and cervical adenopathy. The monospot test was positive for EBV. Serum transaminase levels and coagulation studies became markedly abnormal during the course of this illness. After therapy with fresh-frozen plasma and vitamin K, a cervical lymph node biopsy and unilateral tonsillectomy were performed.

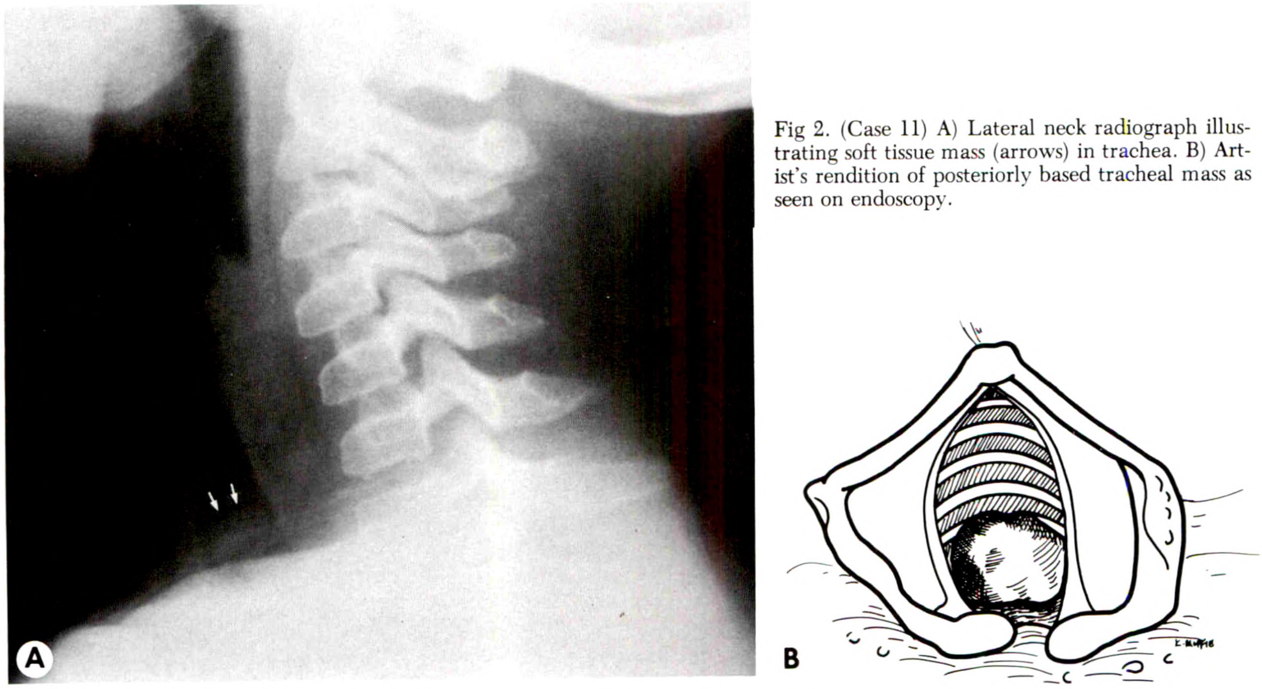

Fig 2. (Case 11) A) Lateral neck radiograph illustrating soft tissue mass (arrows) in trachea. B) Artist's rendition of posteriorly based tracheal mass as seen on endoscopy.

Pathology examination of the tonsil showed a loss of the follicular pattern with replacement by a profuse proliferation of plasma cells, plasmatoid cells, immunoblasts, and histiocytes. A similar lymphoplasmatoid proliferation was seen in the lymph node, with extranodal extension into surrounding fat. Immunocytochemistry on frozen and paraffin-embedded material revealed the infiltrate to consist of polyclonal B cells. The lymph node tissue was strongly positive for EBNA staining.

On the second postoperative day the patient developed diffuse oozing from the tonsillar fossa with subsequent cardiorespiratory arrest. Resuscitation was unsuccessful. Autopsy findings were of disseminated PTLD involving the salivary glands, lungs, gastrointestinal tract, pancreas, kidneys, adrenal glands, bone marrow, and liver.

Case 11. A 10-year-old girl (5 years following liver transplant) developed mononucleosis with EBV-positive serologic findings prior to the onset of biphasic stridor. An intratracheal mass (Fig 2) was debulked during an urgent endoscopic procedure. Sheets of pleomorphic cells, some with plasmatoid features and others with large vesicular nuclei, were noted on microscopy. Despite cessation of immunosuppression, the patient required endoscopic removal of recurring intratracheal lymphoproliferative tumor on four separate occasions. The tracheal lesion was subsequently controlled with regional external beam irradiation. She went on to develop disseminated disease including involvement of the orbit, lung, and liver. Biopsy of the orbit revealed a proliferation of large cells with prominent single to multiple nuclei and frequent mitoses. This lesion was notably more monomorphic than the initial tracheal lesion. Treatment included systemic chemotherapy followed by total body irradiation and bone marrow transplant. She died of sepsis 10 months after presentation with the first intratracheal mass. There was no evidence of residual PTLD on autopsy.

DISCUSSION AND LITERATURE REVIEW

The success of organ transplantation is dependent on immunosuppression to prevent rejection of the transplanted "foreign" tissue. Immunodeficiency, however, is implicated in the pathogenesis of lymphoproliferative neoplasms.[3] The increased risk of lymphomas in patients with congenital immunodeficiency corroborates the significance of this pathogenic factor. Starzl[4] first recognized lymphoproliferative disease as a complication of orthotopic organ transplant in 1968. Initially PTLD was viewed as a non-Hodgkin's lymphoma, but it is now recognized as a spectrum of disorders ranging from benign to malignant in both histopathologic characteristics and clinical course.[1] There is a documented association between primary EBV infection and the development of PTLD.[2]

Epstein-Barr virus infection is also associated with Burkitt's lymphoma, nasopharyngeal carcinoma, and undifferentiated salivary carcinoma; however, it is most commonly recognized as the etiologic agent of infectious mononucleosis.[5] The distribution of the virus is worldwide; primary infection usually occurs in late childhood and adolescence in the United States, with universal exposure by middle adulthood.[6] The virus infects up to 20% of the circulating B-lymphocytes in early mononucleosis. Host defense is primarily by cytotoxic T cells, with some role by interferon and natural killer cells. The "atypical lymphocytosis" of infectious mononucleosis actually consists of a surge in the circulating cytotoxic T cell population. Lifelong latent infection likely represents an equilibrium between viral replication in epithelial cells, B cell proliferation, and T cell control.[7]

Lymphoproliferative disease in immunodeficient patients with EBV infection is postulated to be caused by an absence of T cell control of B cell proliferation — a failure of immune surveillance.[1]

Cyclosporine A has become the mainstay of pharmacologic immunosuppression in the transplant patient. This drug offers rapidly reversible immunosuppression and is largely responsible for the current high survival of both transplant patients and their grafts. It causes a decrease in T cell response, including decreased production of interleukin-2 from T cells, a suppression of the delayed hypersensitivity reaction, and a decrease in cytotoxic T cell activity.[8] Thus, patients receiving CsA who contract EBV infections would be expected to have impairment in controlling the resultant B cell proliferation.

The frequency of PTLD in the pediatric transplant population is approximately 4%. It is much less prevalent in the adult transplant population (less than 1%). The difference in prevalence may be secondary to the increased rate of primary EBV infection in the pediatric population.[9] In fact, EBV serologic findings and DNA typing in this series were consistent with EBV infection in the majority of cases.

Posttransplant lymphoproliferative disease commonly presents in children with lymphoid hyperplasia or masses in the head and neck region in the setting of an acute febrile illness. Otolaryngologists are consulted in the care of these patients for evaluation of airway obstruction, persistent adenotonsillar hypertrophy, suspicious cervical adenopathy, or neck masses. Otitis media or sinusitis may also prompt referral to the otolaryngologist.

Undiagnosed lymphoproliferative involvement of Waldeyer's ring or the trachea can result in catastrophic airway obstruction. Accordingly, aggressive evaluation of persistent head and neck lymphoid hypertrophy is advocated. Tonsillectomy and/or adenoidectomy (or excisional biopsy of other masses obstructing the airway) should be done completely enough to relieve airway compromise. Proper selection of tissue for biopsy and proper handling of the specimen are crucial to avoid misdiagnosis. Results of biopsies of nodes remote from the area of disease can be misinterpreted as nonspecific reactive hyperplasia. Generally, the specimen should be provided fresh and sterile to the pathologist for histopathology, immunophenotyping, determination of cytogenetic markers, viral DNA studies, and bacterial and viral cultures.

Otolaryngologic symptoms are the most common clinical presentation of PTLD; however, approximately 25% of PTLD patients present with gastrointestinal symptoms alone.[1] There is a predilection for involvement of the allograft organ with PTLD. Clinically, this may be confused with rejection.[1] The coagulopathy that developed in case 10 along with other signs of hepatic failure during the patient's progressive severe mononucleosislike illness was secondary to hepatic involvement with PTLD. Liver transplant recipients should have particularly careful monitoring of coagulation status before tonsillectomy and adenoidectomy or other biopsy procedures, with appropriate correction preoperatively.

Erythromycin has been shown to raise CsA serum levels.[10] The administration of this drug should be avoided in any patient receiving CsA unless CsA levels are carefully monitored and other antibiotics are inappropriate. The use of erythromycin may theoretically potentiate the development of PTLD in the transplant patient using CsA who develops a primary EBV infection, by causing increased immunosuppression.

The treatment of PTLD is still controversial. Despite a superficial clinical resemblance to a child with mononucleosis, the child with PTLD requires fundamentally different care. The usual measures to alleviate the course of mononucleosis include steroid administration. Increased steroid dosages in the setting of PTLD may temporarily mask aggressive forms of the disease and are to be avoided. Local surgical procedures are critical for symptoms of acute airway obstruction and offer tissue for pathologic diagnosis.[11] However, as the case of the recurrent intratracheal lesion (case 11) demonstrates, surgical treatment is not curative in PTLD. Drastic reductions in immunosuppression have produced the best survival and were routinely employed by the transplant team at the Children's Hospital of Pittsburgh in the care of the patients presented in this report. Despite this approach, the mortality rate was 25% during a limited follow-up period. In some centers, antiviral agents are emphasized over altered immunosuppression. Irradiation and chemotherapy have been used in patients with progression of disease despite cessation of immunosuppression. Overwhelming sepsis is the major complication in patients treated with systemic chemotherapy and may have been a factor in the death in case 11. Reduction of CsA and other immunosuppressive drugs carries a risk of organ rejection; however, careful reduction of immunosuppression by the transplant team did not result in rejection of the graft organ in any of these 12 patients.

Published series of transplant patients with a diagnosis of non-Hodgkin's lymphoma and other lymphoproliferative lesions following cyclosporine therapy have had mortality rates of over 50%; the inclusion of a greater proportion of mononucleosis-like lymphoproliferative lesions in this report may account in part for the apparently increased survival.[2,3]

CONCLUSION

Posttransplant lymphoproliferative disease is a potentially aggressive lesion that should be suspected in a transplant recipient with persistent lymphoid hypertrophy. Otolaryngologists must be familiar with the head and neck manifestations of PTLD, which may mimic infectious mononucleosis. Administration of erythromycin should be deferred in any patient taking CsA who manifests symptoms compatible with PTLD to avoid raising serum CsA levels at a time when a decrease is indicated. Surgical removal of obstructing lymphoid tissue with proper handling of the specimen offers both definitive diagnosis and relief of upper airway obstruction. Simultaneous tracheotomy is indicated for children with marked airway compromise and coagulopathy. Systemic therapy is required for the treatment of PTLD and will ordinarily include diminution of immunosuppressive agents by the transplant team or pediatrician.

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THE DEAFNESS RESEARCH FOUNDATION
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RHINOVIRUS IN OTITIS MEDIA WITH EFFUSION

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We studied rhinovirus in the middle ear fluid of 61 children with subacute or chronic otitis media with effusion. Rhinovirus was recovered from the middle ear fluid of 5 children with subacute otitis media with effusion. The minimum duration of effusion was 32 to 60 days. Additionally, 1 patient had middle ear fluid that was positive for adenovirus. Bacterial pathogens were cultured from the middle ear fluid of 20 of 61 patients. Our finding that rhinovirus can be isolated from middle ear fluid after an asymptomatic period of several weeks suggests its possible role in the development of otitis media with effusion.

KEY WORDS — adenovirus, otitis media with effusion, rhinovirus.

INTRODUCTION

Otitis media with effusion (OME) is regarded as a multifactorial disease process. Bacterial infection and eustachian tube obstruction are its best-understood pathogenetic factors.[1] Efforts to isolate viruses or detect viral antigens in middle ear effusion of subacute or chronic OME have so far been unrewarding,[2-4] except for one adenovirus-positive case in 60 children.[5] Despite these poor results, increasing circumstantial evidence suggests that viruses may play a role in the causation of secretory otitis media.[3]

We recently managed to isolate rhinovirus in 8% of middle ear effusions and in 18% of nasopharyngeal mucus aspirates in patients with acute otitis media.[6] These observations prompted us to study the role of rhinovirus in the development of OME.

PATIENTS AND METHODS

The study was carried out between November 1987 and January 1988. It included 100 consecutive children who were referred to an otorhinolaryngologist for subacute or chronic OME. During the preoperative 7 days, 35 patients had mild respiratory symptoms, ie, rhinorrhea and cough, reported by the parents; and further, four patients contracted acute otitis media. These 39 patients were thus excluded from the analysis, and 61 patients were left in the study. Otitis media with effusion was defined as the presence of asymptomatic middle ear effusion. The effusion was considered acute with less than 3 weeks' duration, subacute with 3 weeks' to 3 months' duration, and chronic with more than 3 months' duration.[1] The diagnosis of OME was initially made by the referring physician with pneumatic otoscopy. The patients had been followed initially 1 to 3 months before referral,[7] and preoperatively there had been a visit to an otorhinolaryngologist (in general 2 to 3 weeks before operation), who confirmed the diagnosis. The presence of effusion was finally verified by myringotomy at the operation. The duration of the effusion was calculated from the initial diagnosis of OME, which can be considered as minimum duration of effusion.

There were 46 boys and 15 girls. Seven patients were less than 12 months of age, 29 between 1 and 3 years, and 25 patients more than 3 years of age (mean age, 3.2 years; range, 9 months to 12.6 years). The time from the last episode of acute otitis media diagnosed by a physician and from the last episode of upper respiratory tract infection was asked from the parents at the time of the operation. The mean interval between the last episode of acute infection and operation was 25 days (range, 8 to 90 days) for upper respiratory tract infection and 21 days (range, 8 to 90 days) for acute otitis media. Because 25 of the patients had been in close follow-up by an otorhinolaryngologist, the precise minimum duration of effusion could be given: in 25 patients the mean duration of the effusion was 57 days (range, 22 to 113 days). However, in all patients the effusion had been present for at least 3 weeks.

Middle ear fluid samples were collected by myringotomy under general anesthesia for adenoidectomy (in 47 of 61 children) or for insertion of pressure-equalizing tubes (in 58 of 61 children). Middle ear fluid was used for bacterial culture on sheep blood and MacLeod agar and incubated for 48 hours in a carbon dioxide atmosphere at 35°C.

For virus isolation, a cotton swab was dipped in the middle ear fluid sample and placed in a vial containing 2 mL virus transport medium (0.5% bo-

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TABLE 1. PATIENTS WITH VIRUS ISOLATED FROM MIDDLE EAR EFFUSIONS

Sex	*Age (mo)*	*Virus Isolation*	*Bacterial Culture*	*Preoperative Established Minimum Duration of Effusion (d)*
M	12	Rhinovirus	*Streptococcus pneumoniae*	32
M	67	Rhinovirus	Negative	60
M	20	Rhinovirus	Negative	37
F	16	Rhinovirus	Negative	44
M	11	Rhinovirus	*Staphylococcus aureus*	48
F	17	Adenovirus	*Streptococcus pneumoniae*	30

vine albumin in tryptose-phosphate broth containing antibiotics). The virus isolation specimens were immediately frozen on dry ice and stored at −70°C until processed. Virus isolation was done as described earlier, with some modifications.[8] One hundred microliters of each specimen was inoculated into duplicate roller-tube cultures of HeLa Ohio cells and of human fibroblasts. The cultures were stored in a roller device (12 revolutions per hour) at 33°C and examined microscopically every second day. After 6 days of incubation, blind passages were done of negative HeLa cultures, and the passages were incubated for another week. Occasionally a second blind passage was done. Rhinovirus was identified by its typical cytopathogenic effect and lability to acid treatment.

RESULTS

Respiratory viruses were isolated from the middle ear fluid of 6 of 61 (10%) patients with OME: rhinovirus was isolated in five cases, and adenovirus in one case (Table 1).

The mean time from the last episode of acute otitis media or symptomatic respiratory tract infection to surgical intervention was 38 days (range, 18 to 60 days) in the rhinovirus-positive group. The adenovirus-positive patient had her last preceding episode of acute otitis and respiratory tract infection 14 days before operation. The precise onset and duration of middle ear effusion are often unknown. Yet, reasonable assumptions can be made. The mean duration of recorded middle ear effusion was 42 days in the virus-positive group (Table 1). The appearance of the middle ear fluid was mucous in all of these patients, suggesting an extended duration of effusion. All patients with virus in the middle ear fluid received tympanostomy tubes. Ear discharge beginning within a week postoperatively was reported in three of the six virus-positive patients. One of them had a negative middle ear fluid bacterial culture, one showed *Streptococcus pneumoniae*, and one showed *Staphylococcus aureus*.

Middle ear effusion was present in 104 ears of the 61 patients at the time of operation. It was mucous in 98 (94%) ears, serous in 2, and purulent in 4. Positive bacterial cultures from middle ear fluid were obtained in 20 (33%) of 61 patients (Table 2). Postoperative otorrhea was reported in 14 (23%) patients (24 ears). In 6 (43%) of 14 patients bacteria were already cultured in the middle ear fluid sample taken at the time of operation. *Hemophilus influenzae* was found in two samples, *S pneumoniae* in two, *Branhamella catarrhalis* in one, and *S aureus* in one. However, no significant differences were found in the rates of postoperative otorrhea in patients with middle ear fluid positive or negative for bacteria or viruses.

TABLE 2. BACTERIA ISOLATED FROM 61 MIDDLE EAR EFFUSIONS

Strain	*No. of Isolates*	*%*
Hemophilus influenzae	11	18
Staphylococcus aureus	5	8
Streptococcus pneumoniae	4	7
Branhamella catarrhalis	2	3
Negative	41	67

One patient had concomitant *H influenzae* and *S pneumoniae*, and one *H influenzae* and *S aureus*.

DISCUSSION

Increasing evidence suggests that respiratory viruses play an important pathogenetic role in acute otitis media. Four recent studies have found respiratory virus in the middle ear fluid of 11% to 23% of patients with acute otitis media.[7,9-11] On the other hand, acute otitis media has been diagnosed in 57% of respiratory syncytial virus (RSV), 35% of influenza A virus, 33% of parainfluenza type 3 virus, and 30% of adenovirus infections in hospitalized pediatric patients.[12]

In a study of rhinovirus and acute otitis media,[6] we found rhinovirus in the nasopharynx of two patients at the time of diagnosis of acute otitis media. After 2 weeks, when tympanocentesis was done because of poor response to antimicrobial therapy, rhinovirus was isolated from the middle ear fluid. Unfortunately, no typing of the virus strains could be done to exclude reinfection by another virus strain. In the present study, we isolated viruses in the middle ear fluid of 10% of patients with subacute or chronic OME. Rhinovirus was the most common virus isolated from the middle ear fluid samples. This may be explained by the fact that the study was carried out during the rhinovirus season. In addition, the isolation technique used has proved sensitive to rhinovirus from middle ear fluid.[6] During the preceding 6 months RSV, parainfluenza 2, adenovirus, and rhinovirus were the respiratory viruses present in the community. No influenza A or B was diagnosed in that time, and thus the virus isolation method used in the study was not adapted for them. We may have lost some cases of otitis media associated with RSV, since the isolation technique was not optimal for RSV and RSV antigens of middle ear fluid were not studied.

The mean duration of recorded effusion in the middle ear of the virus-positive patients was 42 days, suggesting that a prolonged viral infection might induce OME. An acute respiratory tract infection was not the reason for the viral finding in middle ear fluid, since the mean duration from upper respiratory tract infection was 38 days. However, asymptomatic infection cannot be ruled out. In agreement with these observations, studies on local immunoglobulin A antibodies against respiratory viruses have suggested a possible previous viral middle ear infection in 20% to 50% of patients with OME.[13,14] The seasonal changes of posttympanostomy otorrhea rate suggest an effect due to extrinsic causes such as outbreaks of respiratory tract virus infections.[15]

In 12% to 21% of cases, the middle ear fluid of asymptomatic children harbors bacterial pathogens similar to those identified in acute otitis.[16,17] The most common bacterial finding in mucoid-appearing effusion of chronic otitis media is *H influenzae.*[18] We found pathogenic bacteria in 33% of middle ear fluid samples of patients with OME. Of these, 30% had purulent otorrhea after operation. Further, *S aureus* grew in 8% of samples (Table 2). Some of these may have been contaminated, since the external ear canal had not been sterilized. The presence of pathogenic bacteria in a marked number of ears with postoperative purulent otorrhea suggests that it might be beneficial to perform Gram's stain on and to culture middle ear fluid samples from OME patients undergoing operations and to treat all positive cases with antibiotics for prevention of otorrhea. This approach, however, needs further study.

Our data suggest that in some patients rhinovirus can be isolated from the middle ear fluid after an asymptomatic period of several weeks. The significance of a possible viral infection in the middle ear for the pathogenesis of subacute or chronic OME remains to be clarified.

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PHOTORADIATION THERAPY OF ANIMAL TUMORS AND NASOPHARYNGEAL CARCINOMA

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Both animal tumors and human nasopharyngeal carcinoma were submitted to a photoradiation therapy (PRT) trial in order to determine the efficacy and side effects of PRT, as well as to elucidate its mechanism of cytotoxicity. In animal tumors, the inhibition rate was 70%, and of 20 patients, eight achieved complete remission, and ten, significant remission, with an overall response rate of 90%. The blood picture and the values of serum IgG, IgM, IgA, and C3 all remained stable post-PRT. Only three patients developed mild generalized skin photosensitive reactions, and these did not affect subsequent treatment. There was no immunosuppressive effect as evidenced by a tritium-labeled thymidine–incorporated lymphocytoblast transformation assay performed both before and after PRT. Ultrastructural studies at different time intervals after PRT highly suggested that the mitochondria and rough endoplasmic reticulum were among the first organelles to be damaged.

KEY WORDS — nasopharyngeal carcinoma, photoradiation therapy, tumor.

Since the late 1970s, clinical application of photoradiation therapy (PRT) in cancers of skin, bladder, lung, esophagus, uterine cervix, etc, has been well documented.[1-4] Its use in nasopharyngeal carcinoma (NPC) has not been reported as yet. The purpose of this study was to determine the effectiveness of PRT in animal tumors and the applicability and indication of PRT in NPC, to observe if it has any immunosuppressive effect, and to try to elucidate some aspects of its mechanism of action by making longitudinal electron microscopic studies pre-PRT and at different time intervals post-PRT.

ANIMAL EXPERIMENT

The photosensitizer hematoporphyrin derivative (HpD) was prepared by the Department of Biochemistry and Chemistry, Hunan Medical University. The light source was provided by a helium-neon laser system made by Shanghai Institute of Optics that could emit red light with a wavelength of 632.8 nm. Three quartz fibers were coupled together, with an output power of 90 mW for each. The total output power could be increased to 180 to 200 mW. The animals (C57 mice) and Ehrlich ascites cancer were provided by the Department of Pharmacology, Hunan Medical University.

One hundred mice were divided into five groups at random: an HpD-laser group, a laser group, an HpD group, a normal control group, and a control group with tumor. Every group was inoculated with Ehrlich ascites cancer except the normal control group. Four days later, mice of the HpD-laser group and the HpD group were given intraperitoneal injections of HpD in doses of 5 mg/kg body weight, while those of other groups were injected intraperitoneally with normal saline instead of HpD. Seventy-two hours later, photoradiation was administered with the mice under ether anesthesia and the skin incised in the tumor area with tumor exposed to red light at an intensity of about 90 mW for 30 minutes, the beam spot being 1 cm in diameter. The control group and the HpD group were dealt with in the same way, except that placebo photoradiation was used. Both longitudinal light and electron microscopic studies were made of the tumor tissues biopsied pre-PRT and immediately, 30 minutes, and 3, 6, 12, 24, and 72 hours post-PRT. Four weeks later, the mice were killed painlessly and the tumors were removed and weighed. The inhibition rate of the tumor could be deduced from the following formula:

$$\text{Inhibition rate of tumor} = \frac{\text{tumor weight of control group} - \text{tumor weight of treated group}}{\text{tumor weight of control group}}$$

The thymus also was removed and weighed. A suspension of lymphocytes, prepared from the spleen, was used to perform the lymphocytoblast transformation test with the technique of tritium-labeled thymidine (^{3}H-TdR) incorporation.

Results. The inhibition rates of tumor 4 weeks after PRT are given in Table 1. In 20 mice of the HpD-laser group, there were six complete remissions (no tumor whatever detected macroscopically) and 14 significant remissions (the tumor weight reduced by more than 60%). The mean weight of tumor of the HpD-laser group was 1.32 ± 0.71 g,

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TABLE 1. INHIBITION RATES OF TUMORS 4 WEEKS AFTER PHOTORADIATION THERAPY

	No. of Animals	*Mean Weight of Tumor ±SD (g)*	*Inhibition Rate (%)*	*p*
HpD-laser group	20	1.32±0.71	70	<.01
Laser group	20	4.23±1.06	2	>.05
HpD group	20	4.51±1.01	− 5	>.05
Untreated group	20	4.45±0.97		

HpD — hematoporphyrin derivative.

and a 70% inhibition rate was obtained. The tumors of the laser group and the HpD group showed no response and grew as rapidly as those of the untreated control group.

The mean weight of the thymus and the stimulation index of lymphocytoblast transformation of each group obtained 4 weeks after PRT are summarized in Table 2. The weight of the thymus and the stimulation index of lymphocytoblast transformation of mice inoculated with tumor were significantly lower than those of normal mice ($p<.05$). The weight of the thymus and the stimulation index of lymphocytoblast transformation of mice treated by PRT were slightly higher than those of untreated mice inoculated with tumor; however, the difference was not significant ($p>.05$).

Light microscopic study showed no significant change in either tumor cells or interstitial tissue until 3 hours after PRT, when the cytoplasm of the tumor cells revealed uniform intense basophilia and vacuolization that became even more pronounced 6 hours later (Fig 1B). Twelve hours later (Fig 1C), some of the tumor cells appeared to be necrotic and there was slight edema in the interstitial tissue. Seventy-two hours later, the outlines of the tumor cells were no longer recognizable, indicating that all of the tumor cells were damaged.

The electron microscopic features of the tumor cells pre-PRT (Fig 2A) were cells of various shapes (oval, round), the presence of mitochondria, well-defined rough endoplasmic reticulum, abundant ribosomes, and nuclei of various shapes and sizes. Thirty minutes post-PRT (Fig 2B), the mitochondria and rough endoplasmic reticulum appeared slightly swollen and dilated. The swelling and dilatation became pronounced and the electron density tended to be high 3 hours post-PRT (Fig 2C), but the outer and inner membrane remained intact. So were its crista, although the ribosomes were somewhat reduced. Six hours post-PRT (Fig 2D), with the development of cytoplasmic vacuolization, neither the mitochondria nor the rough endoplasmic reticulum could be recognized any longer. Ribosomes were also markedly reduced. Cell membrane, nuclei, and chromatin showed no definite change. Twelve hours post-PRT (Fig 2E), the plasmalemma was disrupted, with its material spilling out; part of the nuclear membrane also had disintegrated and the chromatin became clumped. Seventy-two hours after PRT (Fig 2F), no tumor cells could be delineated, and the whole field was full of cell fragments.

CLINICAL TRIAL

Twenty NPC patients were enrolled in this study. Sixteen were men and four were women, with ages ranging from 37 to 61 years. Among them, nine patients presented with untreated tumors; 11 had recurrent tumors after previous radiotherapy. Nineteen cases were confirmed pathologically as poorly differentiated squamous cell carcinoma, and one was undifferentiated cell carcinoma.

The materials used were the same as those in the animal experiment. After testing negative on a skin test for HpD sensitivity, each patient was infused intravenously with HpD (at a dosage of 5 mg/kg) in 200 to 300 mL of normal saline, at a speed of approximately 70 to 80 drops per minute. Forty-eight hours thereafter, photoradiation was started by introducing either transorally or transnasally into the nasopharynx a specially designed laser probe 400 μm in caliber, which was connected with the optical fibers. Each light spot was about 1 cm in diameter, and the illumination lasted for 30 minutes. The same procedure was repeated at 72 hours after injection of HpD. If there was no significant response to the initial course of HpD, additional courses were instituted at 2-week intervals with a decreased dosage (2.5 mg/kg) until no tumor was detected macroscopically. If there was no response at all, only two courses were given and the patients would be started on a regimen of radiotherapy. The patients were instructed to avoid direct sunlight

TABLE 2. WEIGHT OF THYMUS AND STIMULATION INDEX OF LYMPHOCYTOBLAST TRANSFORMATION 4 WEEKS AFTER PHOTORADIATION THERAPY

	No. of Animals	*Mean Weight of Thymus±SD (g)*	*p**	*p†*	*Mean Stimulation Index±SD*	*p**	*p†*
Normal control group	20	52.43± 6.13			15.1 ±6.06		
Untreated group	20	41.92± 9.79	<.01		9.49±4.53	<.01	
HpD-laser group	20	44.54±11.77	<.05	>.05	10.96±4.68	<.05	>.05
HpD group	20	42.43±11.90	<.01	>.05	9.97±4.28	<.01	>.05
Laser group	20	40.66±10.58	<.01	>.05	9.47±4.27	<.01	>.05

HpD — hematoporphyrin derivative.

*Versus normal control group.

†Versus untreated group.

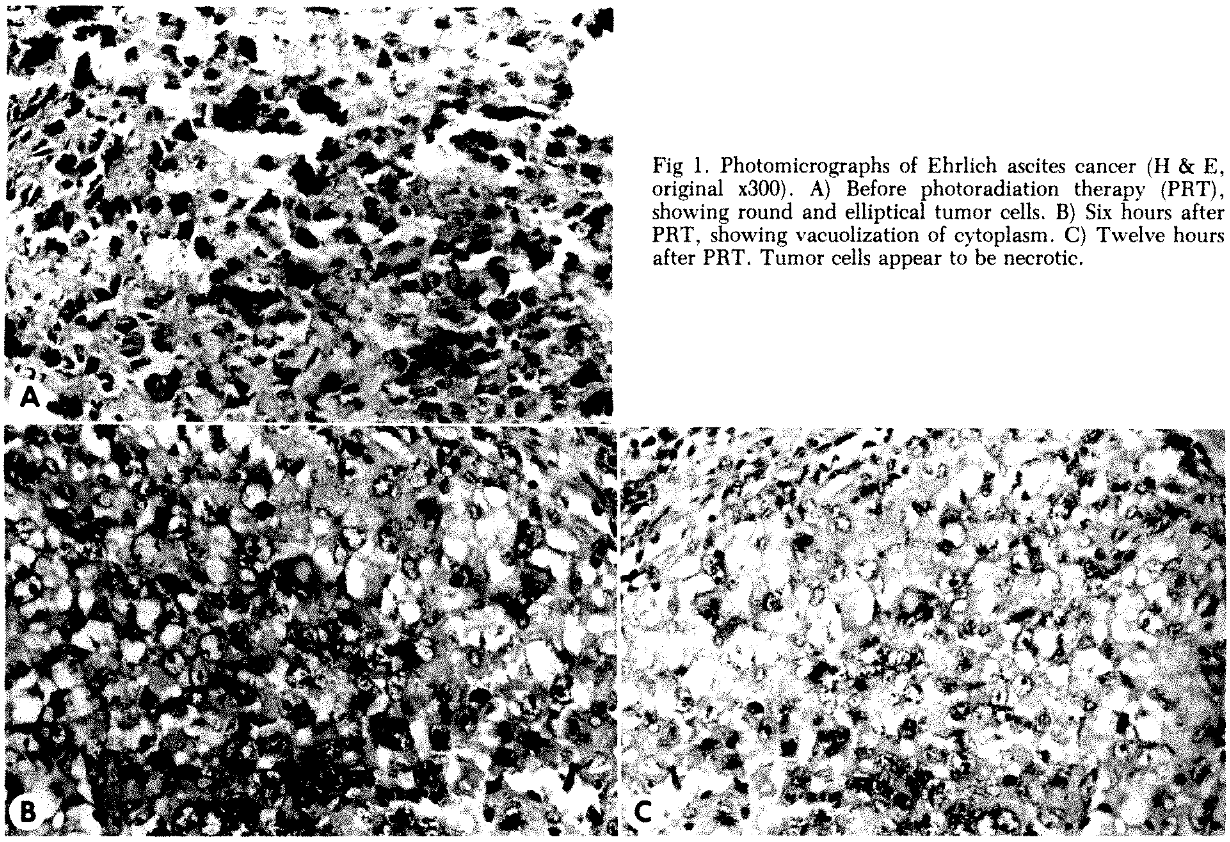

Fig 1. Photomicrographs of Ehrlich ascites cancer (H & E, original x300). A) Before photoradiation therapy (PRT), showing round and elliptical tumor cells. B) Six hours after PRT, showing vacuolization of cytoplasm. C) Twelve hours after PRT. Tumor cells appear to be necrotic.

exposure both during treatment and for 1 month after treatment. Routine blood examination and liver and kidney function tests were done both pre-PRT and post-PRT. A single radial immunodiffusion test was used to determine the values of serum IgG, IgA, IgM, and C3. As a parameter of cell-mediated immune function, an in vitro lymphocytoblast transformation test by a technique of ^{3}H-TdR incorporation was carried out on eight NPC patients both pre-PRT and post-PRT, on 25 healthy subjects, on 33 patients with untreated tumors, and on 22 patients just after irradiation. The last three groups were used as controls.

Both longitudinal light and electron microscopic studies were made of the tumor tissues sampled for biopsy pre-PRT and 30 minutes and 6, 12, 24, and 72 hours post-PRT.

The responses were evaluated in accordance with the following criteria:

1. Complete remission: no tumor whatever could be detected macroscopically.
2. Significant remission: the volume of the tumor was reduced by more than 60%.
3. Partial remission: the volume of the tumor was reduced by less than 60%.
4. No change: no tumor reduction could be detected.

Results. Twenty patients were treated with a total of 66 courses of PRT (average, 3.3 courses each). The tumor responded first by local erythema and edema at the tumor site within 3 to 4 hours after PRT and usually progressed to necrosis 24 hours thereafter. There was complete remission in eight, significant remission in ten, and no change in two cases. All of them have been followed up for $2\frac{1}{2}$ to $4\frac{1}{2}$ years, with 12 cases being followed up for over 3 years. The results remain stable. Among the 11 patients with recurrent tumors after previous radiotherapy, six showed complete remission. The one patient with bilateral cervical metastasis received irradiation of the cervical metastasis in addition to PRT of the primary tumor. As a result, both primary tumor and cervical metastasis subsided completely.

There was essentially no change of the blood test results or liver and kidney function either during or after PRT, except for three patients who developed mild generalized skin photosensitive reactions that did not interfere with subsequent treatment. One illustrative case was that of a 51-year-old man who had recurrent NPC 2 years after radiotherapy. The tumor was located at the left Rosenmüller's fossa and was confirmed pathologically as poorly differentiated squamous cell carcinoma. There was no evident tumor at the treated area after two courses of PRT, and the patient still did well after a follow-up of more than 3 years.

As shown in Table 3, there was no significant change in the values of serum IgG, IgA, IgM, and C3 after PRT.

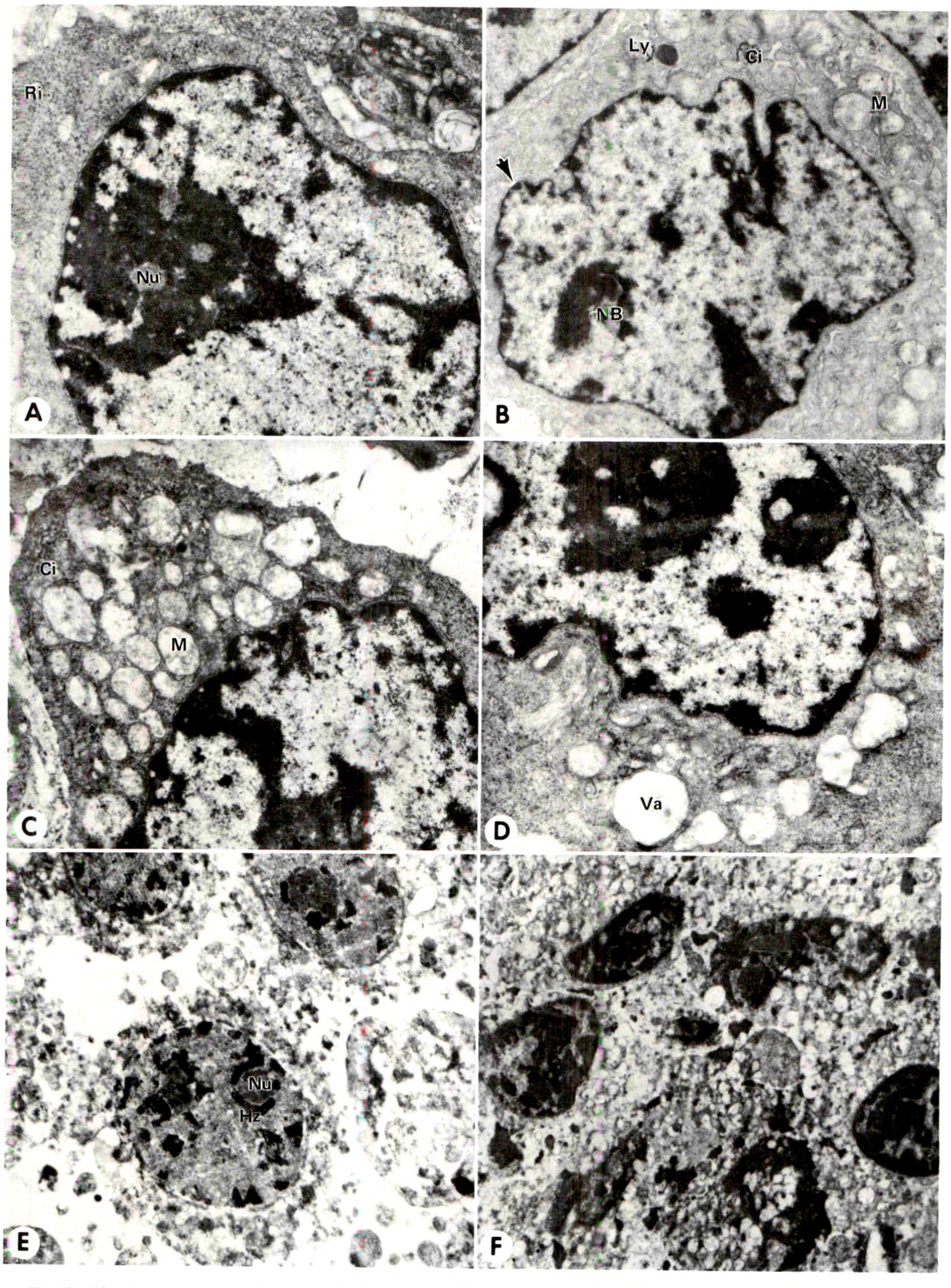

Fig 2. Electron micrographs of Ehrlich ascites cells. A) Before photoradiation therapy (PRT), showing abundant ribosomes (Ri) and large nucleolus (Nu) (original x13,600). B) Thirty minutes after PRT (original x10,000). Mitochondria (M) and rough endoplasmic reticulum cisterna (Ci) appear slightly swollen and dilated (arrow). NB — nuclear inclusion body, Ly — lysosome. C) Three hours after PRT (original x15,600). Swelling and dilatation of mitochondria (M) and rough endoplasmic reticulum cisterna (Ci) are pronounced. D) Six hours after PRT (original x13,600). Vacuolization (Va) of cytoplasm is present. E) Twelve hours after PRT (original x7,600). Plasmalemma is disrupted, with its material spilling out, and part of nuclear membrane has disintegrated, with presence of heterochromosome (Hz) and nucleolus fragments (Nu). F) Seventy-two hours after PRT (original x7,600). Part of nuclear membrane has disintegrated, and chromatin is clumped.

As expected, the stimulation index of lymphocytoblast transformation of untreated NPC patients was significantly lower than that of healthy control subjects ($p < .05$). However, it remained essentially unchanged even after multiple courses of PRT. This result was in sharp contrast with that found in irradiated patients, who showed a significantly lower stimulation index than before irradiation (Table 4).

TABLE 3. VALUES OF SERUM IGG, IGA, IGM, AND C3 BEFORE AND AFTER PHOTORADIATION THERAPY

		Mean Serum Value ± SD (mg/mL)		
	No. of Cases	*Before PRT*	*After PRT*	*p*
C3	11	1.33 ± 0.40	1.35 ± 0.17	> .05
IgG	11	14.95 ± 3.40	17.23 ± 7.47	> .05
IgA	11	2.89 ± 0.64	2.96 ± 0.71	> .05
IgM	11	1.72 ± 0.84	1.49 ± 0.40	> .05

PRT — photoradiation therapy.

The results of light and electron microscopic study (Figs 3 and 4) were the same as those observed in the animal experiment.

DISCUSSION

Nasopharyngeal carcinoma is one of the most frequent malignant tumors in the south of China. In spite of many therapeutic modalities hitherto reported in the literature, radiotherapy remains its primary therapeutic modality, with an average of about a 45% 5-year survival rate.[5-7] Many problems involving a considerably high incidence of local recurrence and/or distant metastases as well as postirradiation sequelae need to be solved. It is desirable to search for a new effective therapeutic modality with less severe side effects either as a primary or as a supplementary mode of treatment for NPC.

TABLE 4. STIMULATION INDEX OF LYMPHOCYTOBLAST TRANSFORMATION IN DIFFERENT GROUPS OF SUBJECTS

	No. of Cases	*Mean Stimulation Index ± SD*
Before PRT	8	41.04 ± 14.57[a]
After PRT	8	50.06 ± 24.69[b]
Healthy subjects	25	71.77 ± 34.27[c]
Untreated NPC	33	50.46 ± 24.69[d]
Irradiated NPC	22	14.92 ± 8.99[e]

a versus *b*, p > .05.
c versus *d*, p < .05
d versus *e*, p < .001.
PRT — photoradiation therapy, NPC — nasopharyngeal carcinoma.

Hematoporphyrin derivative is a photosensitizer that has a special affinity for tumor tissue. It is, therefore, much more concentrated in tumor than in normal tissue 48 to 72 hours after intravenous infusion. Hematoporphyrin derivative taken up by the tumor tissue and activated by a laser beam of 630-nm wavelength can produce singlet oxygen that can destroy tumor cells.

From our preliminary animal experiment and clinical trial it is evident that PRT is highly effective in destroying tumor cells of animal tumors and NPC. As noted in our cases, there were no side effects related to PRT, except in three patients, who developed a mild generalized skin photosensitive response that did not affect subsequent treatment.

Whether or not there is any compromise of host

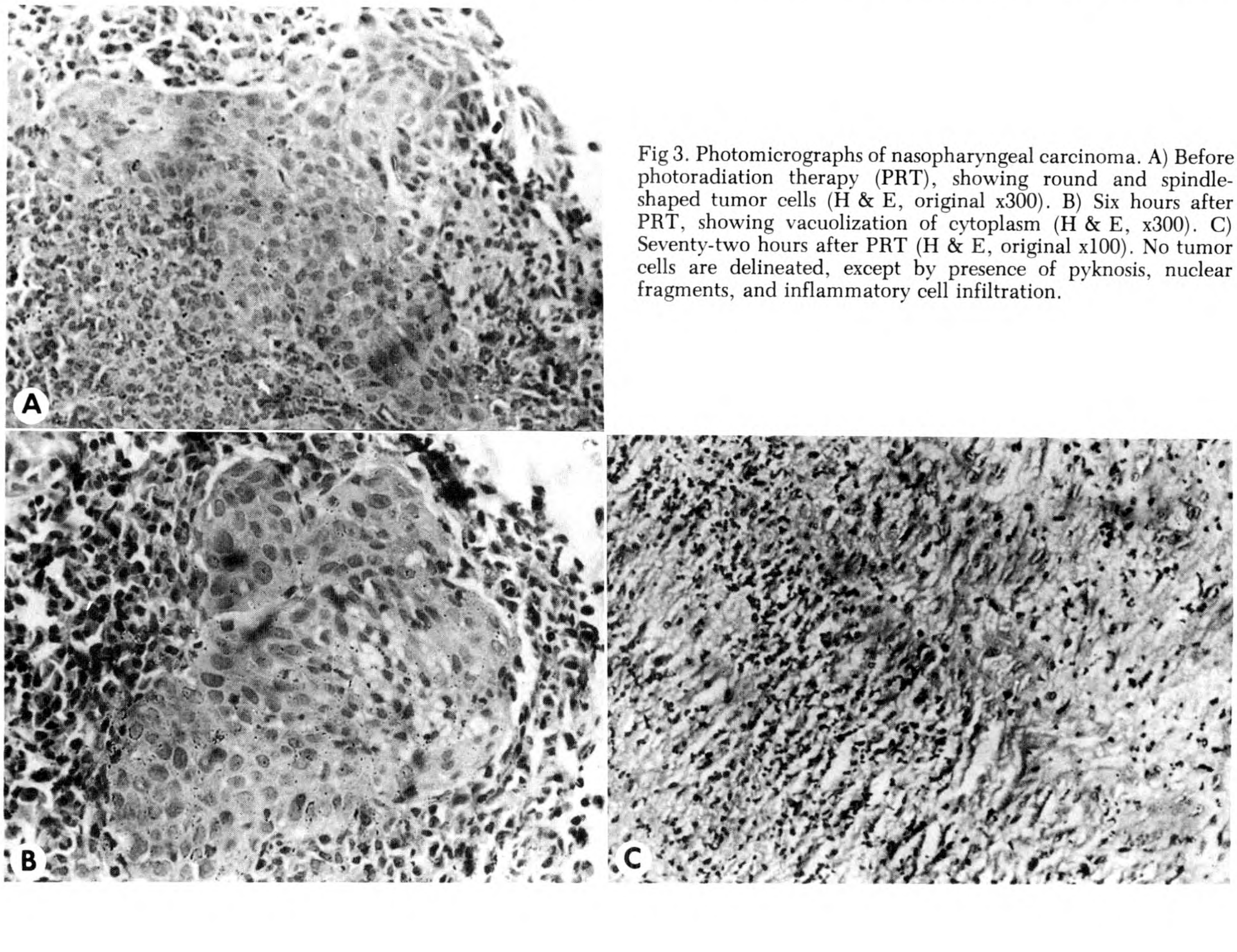

Fig 3. Photomicrographs of nasopharyngeal carcinoma. A) Before photoradiation therapy (PRT), showing round and spindle-shaped tumor cells (H & E, original x300). B) Six hours after PRT, showing vacuolization of cytoplasm (H & E, x300). C) Seventy-two hours after PRT (H & E, original x100). No tumor cells are delineated, except by presence of pyknosis, nuclear fragments, and inflammatory cell infiltration.

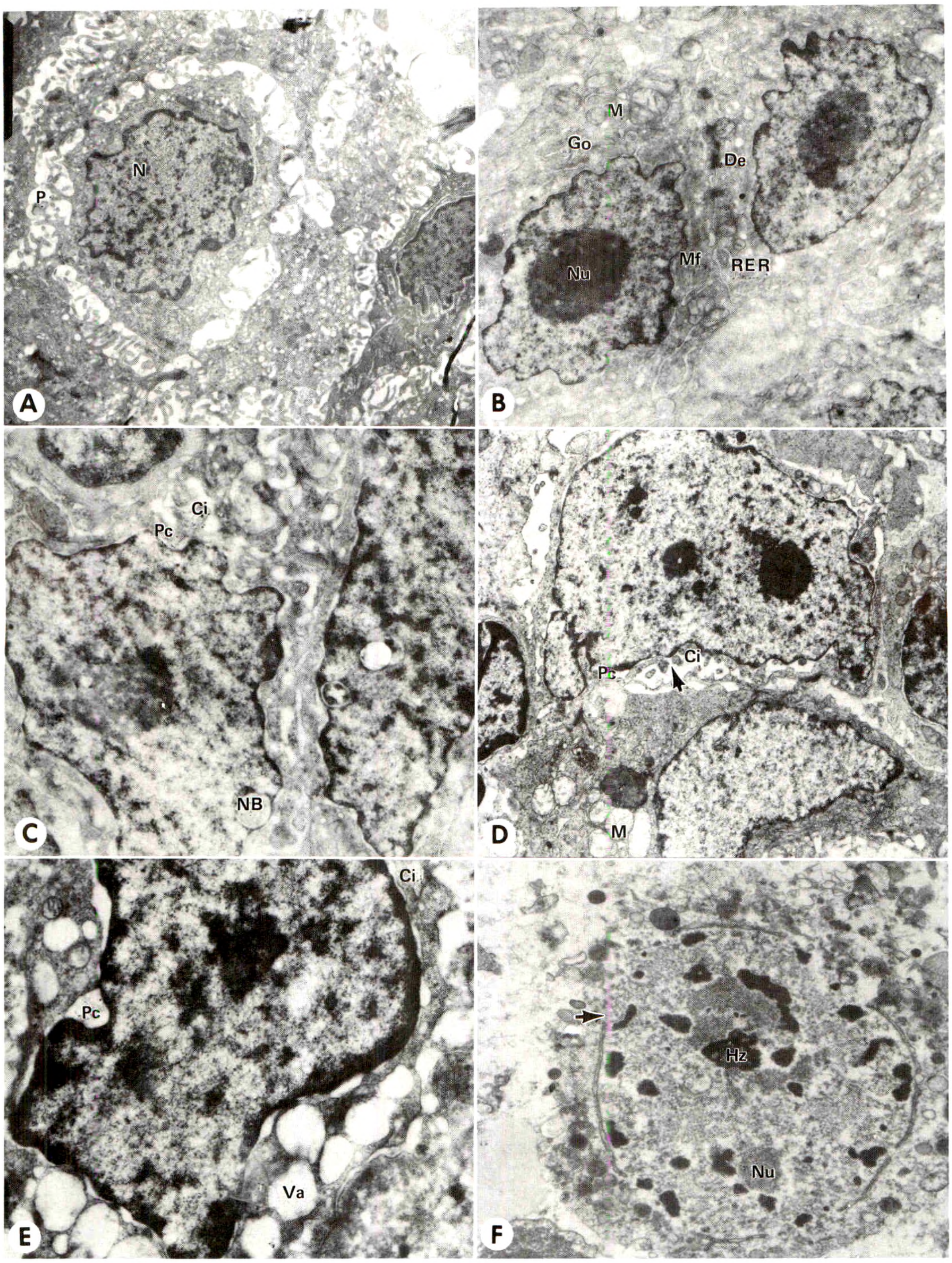

Fig 4. Electron micrographs of nasopharyngeal carcinoma. A) Before photoradiation therapy (PRT), showing multiple indentations of nucleus (N) and fingerlike processes (P) of plasmalemma (original x7,200). B) Before PRT, showing large nucleolus (Nu), well-developed Golgi complex (Go), mitochondria (M), microfilament (Mf), rough endoplasmic reticulum (RER), and desmosome junction (De) (original x9,600). C) Thirty minutes after PRT (original x13,000). Part of rough endoplasmic reticulum cisterna (Ci) and perinuclear cisterna (Pc) are slightly dilated, and nuclear inclusion bodies (NB) are present. D) Three hours after PRT (original x9,000). Both mitochondria (M) and rough endoplasmic reticulum cisterna (Ci) are swollen, as was perinuclear cisterna (Pc), which communicates freely (arrow) with Ci. E) Six hours after PRT, showing vacuolization (Va) of plasma and marked dilatation of both rough endoplasmic reticulum cisterna (Ci) and perinuclear cisterna (Pc) (original x17,000). F) Twelve hours after PRT (original x12,000). Nuclear membrane is partly broken (arrow), with presence of heterochromosome (Hz) and nucleolus fragments (Nu). Plasmalemma is lost, with pouring out of intracellular material, although outline of cell is barely visible.

immune function after PRT has not yet been reported, except by Liang et al,[8] who studied only the effect of HpD, and not the combined effect of HpD plus laser. They demonstrated that there was an intensifying effect on the immune function of mice and that with an increase in dosage of HpD from 10 mg/kg to 20 mg/kg, an immunosuppressive effect could ensue. Our preliminary data showed that PRT had no noticeable effect on the host's immune function, but that radiotherapy did. It is well known that immune function is closely related to the development, progression, metastasis, and relapse of the cancer. Obviously, PRT is far superior to radiotherapy in terms of immune function conservation. Hence, under certain circumstances, PRT might be the only therapeutic modality of choice for some immunocompromised patients with persistent, recurrent, and advanced cancer.

The mechanism of tumoricidal effect of PRT has been widely studied, but so far no definite conclusion or universal agreement has been achieved. Weishaupt et al[9] have hypothesized that the cytotoxicity of activated HpD probably results from the intracellular formation of singlet oxygen (a briefly existing and highly reactive state of the oxygen molecule) when cell-uptaking HpD is exposed to visible light. This theory was confirmed later by many investigators, but the exact sequence of the intracellular changes remains unclear. Precise determination of the intracellular location of HpD in a transplanted tumor by direct visualization of the specific fluorescence showed an accumulation of the compound in the soluble fraction rather than in the nucleus,[10] and Allison et al[11] reported that since the membrane system including cell membrane, nuclear membrane, mitochondria membrane, and lysosome membrane accumulated most of the HpD, they were inevitably the first organelles that would be damaged by the combined action of HpD and laser. It also has been reported that there was less HpD in the tumor cells than in the stroma.[12] After PRT, oozing and blockage of blood vessels occurred, and tumors were thereby destroyed. This finding led to the speculation that destruction of the tumor cells occurs as a result of the obliteration of the tumor's feeding vessels from the stroma. Our results highly suggest that the mitochondria and rough endoplasmic reticulum have a greater affinity for HpD and might be the first organelles to be damaged by PRT, followed by destruction of cell membrane and nuclear membrane. While the mitochondria, which contain abundant enzyme related to energy metabolism of the cell, are actually an energy-providing center, the rough endoplasmic reticulum is mainly involved in protein synthesis. Once the two essential organelles are damaged, the tumor cell will inevitably die by being deprived of essential energy supply and protein synthesis.

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DETECTION OF SPECIFIC IGA ANTIBODIES TO VARICELLA ZOSTER VIRUS IN SERUM OF PATIENTS WITH RAMSAY HUNT SYNDROME

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Varicella zoster virus (VZV)–specific IgG and IgA antibody titers were determined in serial serum samples of 23 patients with Ramsay Hunt syndrome by the immunoperoxidase assay. Varicella zoster virus–specific IgG antibodies were found in the first serum samples of all the patients. In 80% of 20 patients in whom a serum sample was available within 5 days after the onset of the disease, VZV-specific IgA antibodies were detected. The second serum sample was VZV-specific IgA–positive in all of the patients. While all the healthy age- and sex-matched control subjects had VZV-specific IgG antibodies, VZV-specific IgA antibodies were detected in a low titer (dilution = 2) in only three of the subjects. By using VZV-specific IgA antibody titers of ≥2 and ≥4 by the immunoperoxidase assay as a "cutoff" for younger and older patients with Ramsay Hunt syndrome, respectively, an early diagnosis of the disease can be obtained in 89% of the younger and in 64% of the older patients by a single serum sample.

KEY WORDS — IgA antibodies, immunoperoxidase technique, Ramsay Hunt syndrome, varicella zoster virus.

In 1907, Ramsay Hunt described the syndrome that bears his name as being characterized by facial palsy accompanied by otic vesicles and auditory symptoms.[1] It is well known that this syndrome is caused by the varicella zoster virus (VZV).[1-5] The appearance of otic vesicles may precede, accompany, or follow the motor paralysis. Sometimes atypical Ramsay Hunt syndrome is classified as acute peripheral facial palsy (APFP) when patients show only paralysis of the facial nerve but no herpetic eruption. This is recognized as zoster without eruptions.[2-4]

Definitive diagnosis of VZV infection is made by isolation and characterization of the virus,[6] detection of specific viral antigens,[7] or by DNA hybridization.[8] Since these methods are not always available in each institution, the availability of a serologic assay might be of value in the diagnosis of Ramsay Hunt syndrome.

Early diagnosis by a sensitive serologic method should be also of clinical value, since early initiation of steroid therapy may avoid sequelae or may alter the course of posttherapeutic neuralgia.[9,10]

In this study we examined the feasibility of using specific serum VZV-IgA antibodies determined by immunoperoxidase assay[11] in the early diagnosis of Ramsay Hunt syndrome.

MATERIALS AND METHODS

Patients. The study is based on 23 patients with Ramsay Hunt syndrome seen during a 5-year period in the Department of Otolaryngology, Soroka Medical Center. Otolaryngologic and neurologic examinations and audiovestibular investigations were performed.

The study group consisted of 13 females and ten males ranging in age from 6 to 69 years (mean age, 38.2 years). The distribution of patients by age and sex is presented in Fig 1, which shows peak morbidity in the fifth decade.

Among the 23 patients who presented with APFP, 18 manifested herpetic eruptions on the auricle and external ear canal, and one patient in the external ear canal and in the dermatome corresponding to the mandibular division of the trigeminal nerve. Four patients had no eruptions (zoster *sine* herpete) and were diagnosed as having zoster infection through VZV serologic examination based on a fourfold rise of specific VZV IgG and IgA antibodies in paired sera taken in the acute and convalescent stages of the disease.[12] Two patients had involvement of the vestibulocochlear nerve that was manifested by sensorineural hearing loss in one patient and vertigo in the other.

Blood Samples. Serial blood samples were collected from the patients approximately at 2-week intervals, and from age- and sex-matched healthy control subjects. All serum samples were stored at −20°C at the Virology Unit, Soroka Medical Center, until used.

From the Department of Otolaryngology and Head and Neck Surgery (Hadar, Sidi), Beilinson Medical Center and Sackler School of Medicine, Tel-Aviv University, Petah-Tiqva, Israel; and the Department of Otolaryngology (Tovi) and the Epidemiology (B. Sarov) and Virology (I. Sarov) Units, Soroka Medical Center and Faculty of Health Sciences, Ben Gurion University of the Negev, Beer-Sheva, Israel.

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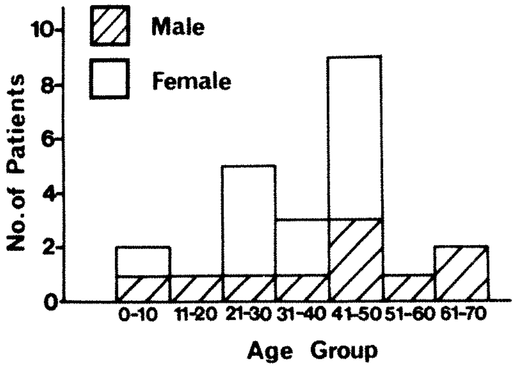

Fig 1. Distribution of patients with Ramsay Hunt syndrome by age and sex.

Immunoperoxidase Test. The sera were tested for specific IgG and IgA to VZV by the indirect immunoperoxidase antibody-membrane antigen (IPAMA) technique. This technique was carried out as described previously.[11,13] Human embryonic fibroblasts were grown in minimum essential medium (Biolab, Jerusalem) supplemented with 10% fetal calf serum (Gibco Biological Co, Grand Island, NY), 1% glutamine (Biolab), 100 U of penicillin/mL, and 200 μg of streptomycin/mL, pH 7.2.

The cells were infected with VZV (Nurit strain, isolated in 1973 from a patient with chickenpox). Infected cultures were incubated at 35°C in minimum essential medium supplemented with 2% fetal calf serum at pH 8.0 until cytopathic effects were observed in 60% to 80% of the cells (24 to 48 hours after inoculation).

Cells were removed from the glass with trypsin Versene solution (Biolab) and washed with 0.01 mol/L phosphate-buffered saline (PBS), pH 7.4. Drops of twice-washed cell suspension containing 10^6 infected cells/mL mixed with 2 x 10^5 uninfected cells/mL were placed on glass slides, dried at room temperature (about 24°C), and acetone fixed. The slides were stored at -20°C. Stored slides were thawed and covered with twofold dilutions of test serum or control serum. After incubation at 37°C for 30 minutes and followed by 15 minutes in PBS, slides were incubated for an additional 30 minutes with anti-human IgA peroxidase conjugate (specific for alpha chain, Dako, Copenhagen) and diluted 1:20 in PBS. After washing, enzymatic activity was detected. The freshly prepared substrate solution was composed of 4 mg benzidine (Riedel-de Haen, Seelze-Hannover, FRG) dissolved in 0.5 mL acetone, 9.5 mL PBS, and 10 μL hydrogen peroxide from a 33% stock solution. Slides were incubated with substrate at room temperature for 5 minutes and were washed with PBS. Each test included known positive and negative sera, and reproducibility of the titration was demonstrated by testing the same positive sera several times.

For detection of VZV-specific IgG, we used anti-human IgG peroxidase conjugate (Miles-Yeda, Rehovot, Israel) diluted 1:80 in PBS instead of using anti-human IgA peroxidase conjugate. The specificity and reproducibility of this method have been shown in previous studies,[11-13] and no cross-reactivity of antibodies with other groups of human herpes viruses was observed.[11,13]

In order to prove that we were detecting IgA and not IgG by the IPAMA technique, we examined cord blood sera and the corresponding maternal sera from 20 healthy VZV IPAMA IgG-seropositive (IgA-seronegative) women for IgG and IgA by the IPAMA technique. Immunoglobulin G antibodies to VZV were detected in the cord blood sera in titers similar to those in the corresponding maternal sera, but VZV IgA antibodies were not detected in the cord blood sera.

Statistical Methods. The Fisher exact test was used to compare the difference in proportions of patients with VZV-specific IgA antibodies versus matched controls. The difference between the geometric mean titers of the patient groups below (and including) 40 years of age and over 40 years of age was tested for statistical significance by Student's *t* test for small samples.

RESULTS

Serum-specific IgG antibodies to VZV were found in the first serum samples of all the patients.

A fourfold rise of specific IgG and IgA antibodies was detected in paired or serial serum samples of all patients in this series, thus indicating a recent reactivation of VZV infection (Fig 2).

Serum-specific IgA antibodies were detected in the first and/or the second serum samples of all patients. In 16 of 20 patients (80%) in whom a serum sample was available as early as 1 to 5 days after the onset of illness (mean, 2.6 days), VZV-specific IgA antibodies were detected. The second serum sample, taken in the convalescent period, was VZV-specific IgA-positive in all patients (Fig 2B).

While matched healthy control subjects tested positive to serum-specific VZV IgG antibodies in a titer range of 2 to 16, only in three (11%) of the control subjects were serum-specific VZV IgA antibodies detected in low titers (dilution = 2). These were healthy control subjects in the fifth to seventh decades of life (47, 50, and 69 years). In the first 5 days after onset of the disease, 89% of the young patients (≤ 40) had VZV-specific IgA antibodies in a titer of ≥ 2 ($p = .0007$), and 64% of the older patients (>40) had VZV-specific IgA antibodies in a titer ≥ 4 ($p = .002$). (None of the control subjects had an antibody titer of ≥ 4.)

Patients over 40 years of age showed a higher level of geometric mean titers for VZV IgA antibody of the higher titer (32 ± 2.9) than the patients below (and including) 40 years of age (15.02 ± 2.06), but the difference was found to be borderline with re-

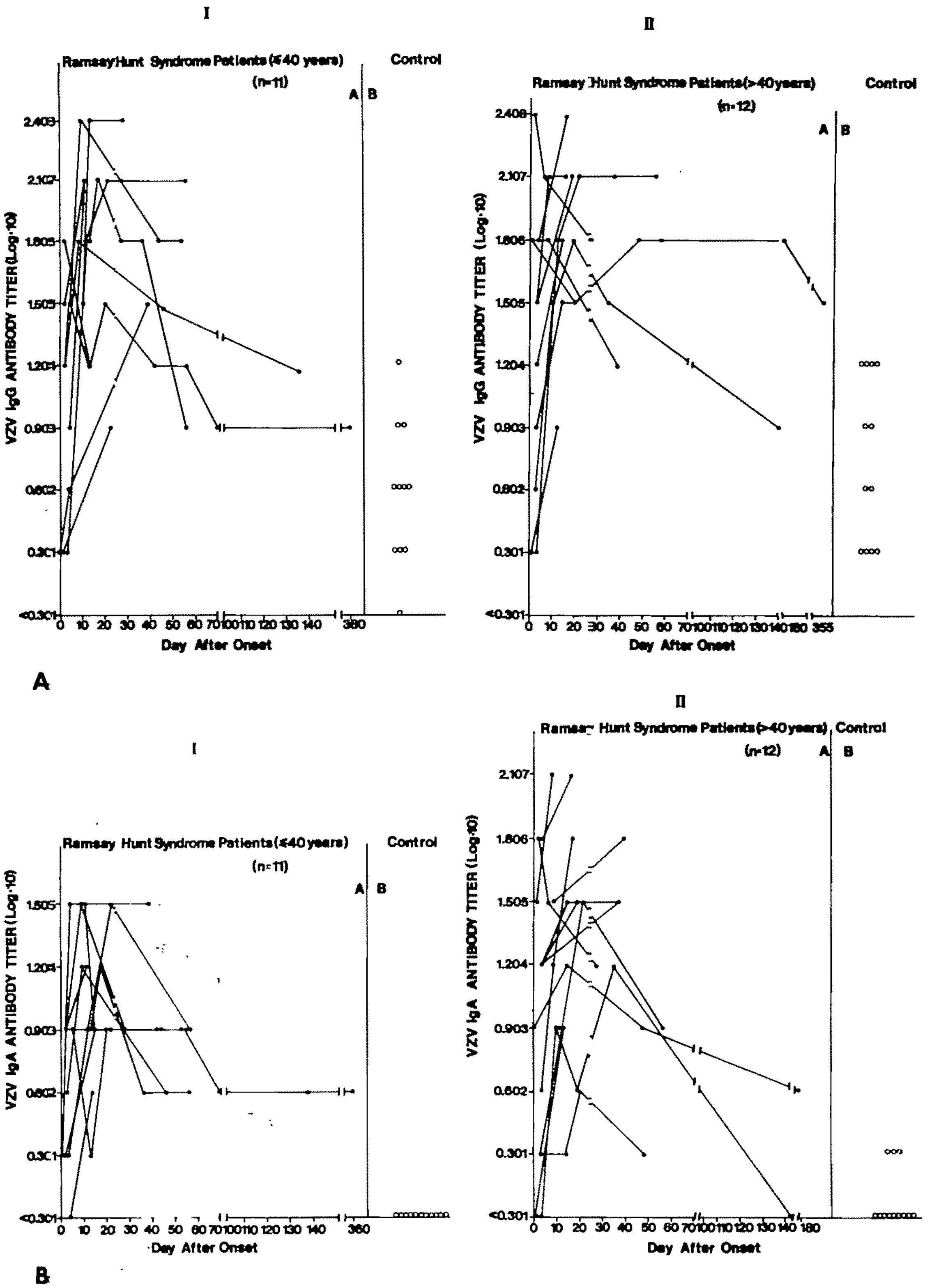

Fig 2. VZV-specific antibodies determined by IPAMA in serial samples of patients with Ramsay Hunt syndrome (A) and in matched controls (B). I — patients 40 years of age and under, II — patients over 40 years of age. A) IgG antibodies. B) IgA antibodies.

spect to statistical significance ($t = 1.98$, $.1 > p > .05$). The older patients (>40) reached the peak titer of IgA antibodies within an average of 17.5 days and the younger patients (≤40) within an average of 13.3 days. These differences between the older and the younger groups might have been affected by a silent reactivation of the VZV in the older group.

Likewise, geometric mean titers for VZV IgG antibody of the higher titer detected were higher in the older patients (82.1 ± 2.5) than in the younger patients (78.9 ± 2.8), but the difference was not significant. The older patients reached the higher titer of IgG antibodies within an average of 19.2 days and the younger patients within an average of 15.8 days.

DISCUSSION

Ramsay Hunt syndrome, or herpes zoster oticus, is a known cause of APFP. The symptoms manifested can include otic vesicles, facial paralysis, hearing loss, dizziness, and severe ear and facial pain.[1-4,10] This syndrome is responsible for 2% to 9% of all APFP.[10] The absence of herpetic eruption (zoster *sine* herpete) is not unusual.[2-4] In our study zoster *sine* herpete occurred in four of 22 patients (18%). Accordingly, in idiopathic peripheral facial palsy (Bell's palsy), zoster must be considered in the differential diagnosis and serologic investigation should be performed.[12]

Definitive diagnosis of zoster is done by isolation of the virus,[6] determination of the specific antigen,[7] DNA hybridization,[8] and serologic assay.[14-19] The last is of value in analysis of cases in which the disease occurs without skin manifestations and in which material for the direct identification of the virus or the antigen is unobtainable. Furthermore, the IPAMA technique is characterized by its rapidity and simplicity.

Various serologic tests are available for assay of antibody to VZV. The most commonly used technique for detection of the specific antibody is the complement-fixing antibody test. This technique has a limited value because of cross-reactivity with herpes simplex infection.[20]

In the past decade immunofluorescent[14] and immunoperoxidase[13] techniques were developed for the detection of serum-specific IgG antibodies to VZV-induced membrane antigen. These antibodies enable the diagnosis of both varicella and zoster infections in paired sera. Recently, a highly sensitive radioimmunoassay[15] and enzyme-linked immunosorbent assay[17] have been used for the detection of VZV-specific IgG antibodies. Today the serodiagnosis of zoster commonly is confirmed by the demonstration of a fourfold rise of VZV-specific IgG antibodies in acute and convalescent stages of the disease. Although determination of VZV-specific IgG antibodies is a sensitive and reliable method of diagnosis, it does not offer the benefit of early diagnosis since it necessitates taking paired or serial samples at about 2-week intervals.

An early marker of the infectious process is the induction of serum-specific IgM antibodies. Although regularly produced in primary varicella infections, serum-specific VZV-IgM antibodies are not present consistently in reactivated infections; therefore, determination of VZV-specific IgM antibodies is not a reliable method of diagnosis in zoster.[18,19]

The function of VZV-specific IgA antibodies is being investigated extensively. Recent studies in rats, mice, and humans suggest that this antibody is involved in the transport of foreign antigens from the circulatory system into the bile.[21] There are several reports of detection of VZV-specific IgA antibody responses in viral infections caused by herpes simplex virus,[22,23] Epstein-Barr virus,[24-26] cytomegalovirus,[27] and VZV,[11,12,16] and all members of the herpes virus group. Virus-specific IgA antibody has been detected in both primary and reactivated VZV infections. Thus, VZV-specific IgA production seems to be not restricted to primary infections but also able to signal reactivation or reinfection.[11,12,16]

Of particular interest is the finding that serum-specific IgA antibodies to Epstein-Barr viral capsid antigen appear at high titers in most patients with undifferentiated or nonkeratinizing types of nasopharyngeal carcinoma and in only 2% of the healthy population. This indicates that IgA antibody titers to viral capsid antigen might have potential clinical value for the diagnosis and management of patients with nasopharyngeal carcinoma.[24-26]

In this study we examined the possibility of whether VZV IgA antibodies detected by immunoperoxidase assay might be an early signal of the reactivated VZV infection and be useful for the early diagnosis of Ramsay Hunt syndrome. Induction of specific IgA antibodies was detected in all patients. This occurred in 16 of 20 patients (80%) in whom the serum sample was available within 1 to 5 days after the onset of the disease.

Concerning the specific IgA seropositivity of the three subjects in the matched control group, these adults (43 to 69 years) might have been affected by a silent reactivation of the VZV that occurs with aging.[28] Indeed, VZV-specific IgA antibody was not detected in any of the matched control subjects below (and including) 40 years of age.

Taking as a cutoff of serum-specific VZV IgA antibody titers of ≥ 2 and ≥ 4 by the indirect immunoperoxidase assay for Ramsay Hunt syndrome patients younger and older than 40 years of age, respectively, an early diagnosis can be obtained in 89% of the younger ($p = .0002$) and in 64% of the older patients ($p = .002$) by a single serum determination of specific VZV-IgA antibody titer. Therefore, determination of VZV-IgA antibodies by the indirect immunoperoxidase assay might be helpful in the early diagnosis of Ramsay Hunt syndrome.

In conclusion, the present study supports the feasibility of using specific VZV IgA antibody as determined by IPAMA in a single serum sample for early and rapid diagnosis of Ramsay Hunt syndrome. This is of particular importance in light of recent reports that suggest that early diagnosis and treatment of Ramsay Hunt syndrome patients with acyclovir might prevent serious long-term permanent disability.[29-31]

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ELECTROMYOGRAPHY OF THE INFERIOR CONSTRICTOR AND CRICOPHARYNGEAL MUSCLES DURING SWALLOWING

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Electromyography (EMG) of the inferior pharyngeal constrictor (IC) and the cricopharyngeal (CP) muscle was recorded in 18 patients with swallowing and/or aspiration problems who were candidates for cricopharyngeal myotomy. The EMG recordings were compared to those of 13 "normal" subjects who did not suffer from such problems. Differences in EMG activity between the control group and the patient group were considered with respect to the clinical symptoms in the patient group. Recording of EMG in the CP and IC muscles is relatively safe, useful, and easily mastered. The technique may provide important information regarding the function of some of the muscles involved in deglutition.

KEY WORDS — dysphagia, electromyography, pharyngeal muscles.

Interest in the role of the cricopharyngeal (CP) muscle in disorders of swallowing has increased greatly in recent years.[1-3] Extensive research has been conducted regarding the anatomy, innervation, and physiology of the upper esophageal sphincter.[4,5] Several studies have been published on the recording of electromyographic (EMG) activity of the CP muscle and other pharyngeal muscles in experimental animals,[6,7] but some of the data are contradictory. Few studies involving humans have been published, and even fewer in the English literature.[8-10] In none of these studies were EMG recordings performed routinely in patients with swallowing problems.

The aim of the present study was to explore the EMG activity of the CP and inferior pharyngeal constrictor (IC) muscles in patients suffering from deglutition difficulties (with or without aspiration). These patients were candidates for surgical treatment by CP myotomy. This presumably would help in the localization of the site of lesion in the swallowing mechanism.

MATERIAL AND METHODS

The normal patterns of EMG activity of the pharyngeal muscles at rest and during deglutition were determined in subjects who were hospitalized in the Department of Otolaryngology of Hadassah University Hospital for reasons other than swallowing or aspiration problems. This "control" group included eight men and five women who were between 30 and 70 years of age (mean, 42 years). The various causes for hospitalization are listed in Table 1. All subjects were screened by clinical history and by a physical examination. None of them suffered from pharyngeal symptoms.

The other group of patients included ten men and eight women between 35 and 75 years of age (mean, 52 years) who were hospitalized in various departments of our hospital and had been referred to our service for evaluation of swallowing and/or aspiration problems and for consideration of CP myotomy. These patients suffered from various neurologic and other conditions, which are summarized in Table 2. This Table shows also the various clinical symptoms within this patient group. An informed consent was obtained from all patients in whom EMG recordings were made.

For the EMG recordings, concentric needle electrodes (EINS2) were used. Lidocaine (1%) was injected superficially under the skin at the puncture site, with care taken not to inject the muscles themselves.

For the CP muscle the needle electrode was passed through the skin in a posterior and medial direction, at the level of and just lateral to the cricoid cartilage. The needle was advanced until it penetrated the CP muscle. When the needle entered the muscle there was a burst of activity — the insertional activity — that diminished gradually, reaching a resting "tonic" level. Functional verification of the location of the electrode was done by asking the patient to swallow and taking note of the change in the EMG activity. Typically, the CP muscle responded by a marked change in its activity only during the act of swallowing and very slightly or not at all during breathing or phonation. In cases in which the lateral cricoarytenoid muscle was penetrated accidentally, the EMG activity increased mainly during phonation. To sample the IC muscle a shorter concentric electrode was used and inserted through the skin after lidocaine infiltration. The puncture was made at the level of the upper border of the thyroid cartilage in a posteromedial direction until the EMG activity (insertional burst) was noticed. Again, activity was increased

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TABLE 1. CAUSES FOR HOSPITALIZATION OF "CONTROL" GROUP OF PATIENTS

Diagnosis	*No. of Patients*
Unilateral vocal cord polyp	6
Unilateral vocal cord paralysis	4
T1 glottic carcinoma	2
Acute laryngitis	1

markedly during the act of swallowing, but was changed minimally or not at all by breathing or phonation. The EMG activity was amplified and displayed on a 1510A Hewlett-Packard electromyograph, which has a frequency band of 15 to 5,000 Hz. A storage oscilloscope was connected to the electromyograph and triggered manually, either randomly to record resting activity or simultaneously with the start of a swallow. The stored EMG traces were photographed with a Polaroid camera.

RESULTS

The normal EMG patterns of the CP and the IC muscles were determined in the "control" group. Whereas the IC muscle exhibited only minimal activity at rest, the CP muscle usually displayed marked resting activity (see Figure, A). When a swallow occurred, the IC muscle revealed a large burst of activity (about 0.5 mV maximal amplitude) lasting about 0.5 to 1 second. Simultaneously with or shortly before the initiation of the burst in the IC muscle, the resting activity of the CP muscle dropped markedly and almost disappeared (see Figure; A,B). It remained low until near the end of the IC burst. Quite often this inhibition of activity in the CP muscle was preceded by a short (20- to 100-millisecond) burst (see Figure, C). Following the period of inhibition the CP muscle exhibited a second, larger and more intense burst ("rebound") lasting about 1 second, with gradual return to the preswallowing level of activity (see Figure; A,C). The EMG spikes of either the IC or the CP muscles reached up to 0.5 mV in amplitude and approximated 2 milliseconds in duration.

Various deviations from the normal patterns were noticed among the patients with swallowing problems. The patients could be divided into five main categories:

1. Patients in whom during swallowing there was only a slight or no increase at all in the EMG activity of the IC muscle (see Figure, D).
2. Patients in whom the "resting" activity in the CP muscle was increased markedly (see Figure, E).
3. Patients in whom no inhibition of activity in the CP muscle could be observed during swallowing, or in whom the drop in activity was smaller than that observed in the normal group.
4. Patients in whom there was abnormal timing between the burst of activity in the IC muscle and the inhibition of the CP muscle (see Figure, F).
5. Patients in whom various combinations of the above disturbances were observed.

Table 3 summarizes the type and the number of pathologic EMG traces among the various patients. It is evident that in patients who suffered from conditions such as motor neuron disease or progressive bulbar palsy, the most common finding was a lack of increased activity in the IC muscle, sometimes combined with abnormal synchronization with the CP muscle. These reflected mainly the weakness of hypopharyngeal contracture. On the other hand, in patients with idiopathic swallowing problems, increased resting (tonic) activity in the CP muscle was the main feature.

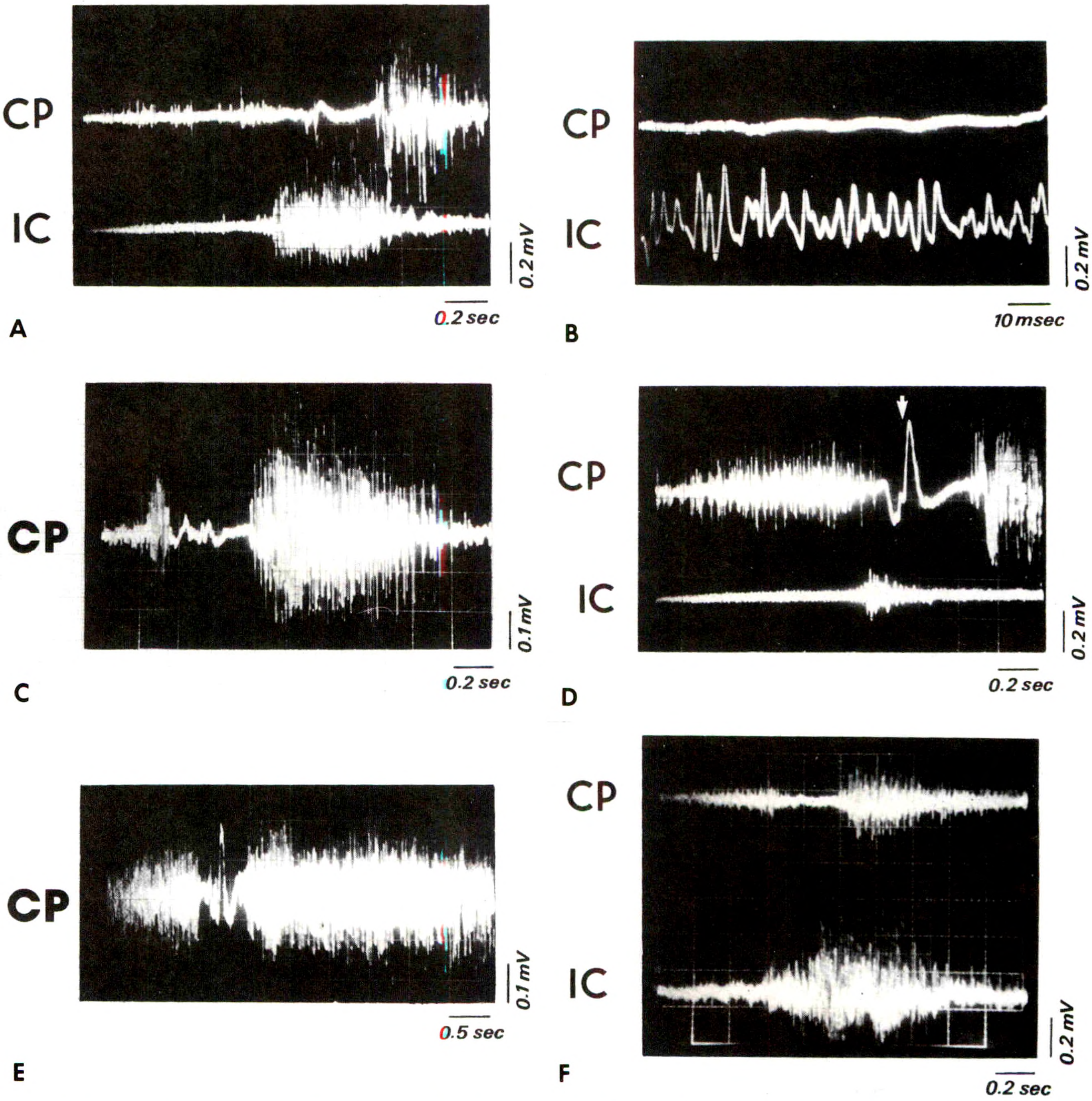
DISCUSSION

There is still a controversy in the literature regarding the role of the CP muscle and the IC muscle in the creation of the upper intraluminal high pressure zone and whether or not these muscles are "at rest" in tonic contraction. It was shown that at least in experimental animals the upper high pressure zone (sphincter) should be attributed in part to the elastic forces of the surrounding tissues and to the forward displacement of the larynx.[7] Moreover, CP myotomy in humans reduces but does not abolish the high pressure zone.[10,11] Doty[12] was even more extreme in concluding that the upper high pressure zone is generated only by passive elasticity of the surrounding tissues.

A tonically contracted striated muscle should be associated with continuous EMG activity. This indeed was found in several studies in experimental animals[6,7] and in a few studies in humans.[5,8,9] In the

TABLE 2. CLINICAL DIAGNOSES AND SYMPTOMS IN DYSPHAGIA GROUP (N = 18)

Diagnosis	*Dysphagia*	*Dysphagia and Aspiration*	*Aspiration Alone*	*Dysphagia and Nasal Regurgitation*
Stroke	1			1
Progressive bulbar palsy		2	1	
Pseudobulbar palsy	1	1		
Parkinson's disease	2			
Myasthenia gravis	1		1	
Motor neuron disease	1	1		1
Multiple sclerosis	1	1		
Idiopathic swallowing problems (cricopharyngeal "spasm")	1	1		



Recordings of EMG activity. A) Of cricopharyngeal (CP) and inferior pharyngeal constrictor (IC) muscles in "normal" subject, before and during act of swallowing. Note "resting" activity in CP muscle, which is almost absent in IC muscle (see text). B) Of CP and IC muscles during swallowing recorded in "normal" subject with short time base. Note intense activity in IC muscle, while CP muscle is completely silent. C) Of CP muscle in "normal" subject before and during swallowing. Note short burst that precedes inhibition phase. D) In patient who suffered from motor neuron disease (amyotrophic lateral sclerosis). Note pathologically increased activity in CP muscle prior to inhibition (arrow). On other hand, there is only slight increase of activity in IC muscle, which corresponds to its weakness. E) Of CP muscle in patient with idiopathic CP "spasm." Note pathologically increased activity before and after act of swallowing (which corresponds to period of inhibition). F) In patient with Parkinson's disease. There is disturbance in synchronization between activity in IC and CP muscles, manifested by prolonged activity in IC muscle overlapping "rebound" in CP muscle.

opossum,[7] the IC muscle also demonstrated continuous spike activity at rest, thus contributing to the upper high pressure zone. In humans, however, only minimal EMG activity was found at rest in the IC muscle.[9]

In the present study, differences in EMG activity between CP and IC muscles were obvious in all the "normal" subjects. For example, the resting activity was much more prominent in the CP muscle than in the IC muscle. Whereas the CP showed a phase of inhibition followed by a rebound burst during deglutition, such inhibition could not be detected in the IC muscle in any of the subjects. Considering also the temporal relationships between the activity in the two muscles (the burst in the IC muscle syn-

TABLE 3. FREQUENCY AND NATURE OF DISTURBED EMG TRACES AMONG PATIENTS WITH SWALLOWING PROBLEMS

EMG Disturbance	*No. of Patients*	*Clinical Diagnosis (No. of Patients)*
Lack of normal increase of EMG activity in IC muscle	4	Motor neuron disease (2); progressive bulbar palsy (2)
Abnormal increased resting activity in CP muscle	2	Idiopathic swallowing problems (2)
Lack of normal inhibition in CP muscle	2	Parkinson's disease (1); pseudobulbar palsy (1)
Abnormal synchronization between IC and CP muscles	3	Multiple sclerosis (1); Parkinson's disease (1); myasthenia gravis (1)
Combination of disturbances	4	Stroke (1); multiple sclerosis (1); motor neuron disease (1); progressive bulbar palsy (1)
Normal	3	Myasthenia gravis (1); stroke (1); pseudobulbar palsy (1)

EMG — electromyographic, IC — inferior pharyngeal constrictor, CP — cricopharyngeal.

chronized with the inhibition in the CP muscle) we conclude that in humans, the IC muscle functions as part of the hypopharyngeal musculature that squeezes the bolus downward, in contrast to the opossum, in which the IC muscle was shown to be a part of the upper esophageal sphincter.[7]

The recording of EMG activity in the IC and CP muscles in patients suffering from swallowing problems was found to be a useful technique for the assessment of the function of these muscles and the deglutition mechanism in general in neurologic conditions. The test is relatively safe, is easy to perform after mastering the technique, and is associated with minimal inconvenience to the patient. The data obtained by this test are important in that they reflect in the most direct way the function of deglutition musculature. The test can reveal directly whether a disorder involves the hypopharyngeal contraction due to lack of increased activity in the IC muscle, CP muscle spasm due to increased resting activity, absence of the mechanical relaxation of the CP muscle due to lack of the normal inhibition of EMG activity during deglutition, or disturbed synchronization between the IC muscle's contraction and the CP muscle's relaxation. In many cases, various combinations of disturbed function were found.

It is not intended that EMG recording should replace the traditional tests that are currently used for the evaluation of swallowing problems. However, we believe that EMG recording of the IC and CP muscles should be added to these tests, as it might improve the localization of the site of lesion and the selection of patients who are most likely to benefit from CP myotomy.

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EXPERIMENTAL ENDOLYMPHATIC HYDROPS: ARE COCHLEAR AND VESTIBULAR SYMPTOMS CAUSED BY INCREASED ENDOLYMPHATIC PRESSURE?

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The correlation between inner ear pressure and cochlear function was investigated in guinea pigs with unilaterally obliterated endolymphatic sacs and ducts. In 11 animals that developed endolymphatic hydrops, auditory thresholds as monitored by auditory evoked action potentials had increased with recruitment. Most of these animals also experienced episodes of spontaneous nystagmus. In control ears endolymphatic pressure did not differ more than 0.5 cm H2O from perilymphatic pressure. In six of 11 hydropic ears, endolymphatic pressure was more than 0.5 cm H2O higher than perilympathic pressure; auditory thresholds in all these ears had deteriorated within 2 weeks before pressure recording. No further hearing deterioration within this period was noted in five hydropic ears with endolymphatic pressure equal to or lower than perilymphatic pressure. Endolympathic-perilymphatic pressure gradients may contribute to auditory threshold increase in endolymphatic hydrops, but are not its only cause.

KEY WORDS — guinea pig, inner ear pressure, Meniere's disease, Preyer's reflex, Reissner's membrane rupture.

INTRODUCTION

The cochlear and vestibular symptoms in Meniere's disease are well known.[1-3] The pathogenesis of the disease, however, still remains a matter of speculation. Operative obliteration of the endolymphatic sac and duct in the guinea pig produces a model of this disease in which many of the cochlear alterations but only sporadic vestibular symptoms can be reproduced.[4-9] The only consistent morphologic finding in patients with Meniere's disease and in the animal model is an enlargement of the endolymphatic space, or so-called endolymphatic hydrops. This distended appearance of the membranous labyrinth often has been considered to represent elevated pressure in the endolymphatic space. There is also evidence that elevated inner ear pressure impairs cochlear function.[10-15] Thus, many current theories on the pathogenesis of Meniere's disease[16-18] presume that there is, at least intermittently, an increased endolymphatic pressure (ELP). Increased ELP, however, has never been demonstrated directly in patients with Meniere's disease.

With the servocontrolled micropipet system,[19] reliable hydrostatic pressure recordings in very small fluid compartments such as the scala tympani and scala media of the guinea pig have become possible. In normal guinea pigs, ELP is approximately equal to perilymphatic pressure (PLP), and in all situations in which inner ear pressure has been altered acutely by different manipulations, both ELP and PLP changed concomitantly.[20-22] Even in experimental endolymphatic hydrops, Long and Morizono[23] and Matsubara et al[24] found very similar PLP and ELP. Higher ELP than PLP in individual ears has been reported to date only in one small series of guinea pigs 3 months after obliteration of the endolymphatic sac.[25]

The present study was designed to investigate whether there is a correlation between inner ear pressure and alterations of cochlear and vestibular function in the guinea pig model of endolymphatic hydrops.

METHODS

Thirty-five pigmented guinea pigs weighing 400 to 800 g with normal Preyer's reflex thresholds[26] were used; 15 of them provided reliable data. With anesthesia produced by intramuscular ketamine hydrochloride (Ketalar 40 mg/kg) and xylazine (Rompun 8 mg/kg), silver ball electrodes were implanted on the round window membranes in both ears, and a stainless steel screw electrode was inserted into the skull at the vertex as a reference. Screw electrodes also were placed at the anterior and posterior border of the right orbit for recording horizontal eye movements. All electrodes were attached to a small connector (Amphenol) that was fixed to the skull with dental cement. The endolymphatic sac and duct on one side were obliterated with bone wax by use of an extradural posterior fossa approach.[27]

Regular auditory and vestibular tests were performed in the awake animal at least once every 10 days. In a soundproof room, the guinea pig was placed in a small box with only the head exposed and with the head fixed (similar to Aran and Erre[28]). For cochlear stimulation, clicks and tone bursts of 1, 2, and 4 kHz (four cycles, 4- to 1-millisecond duration) were applied in a closed system with a small earphone placed on the pinna. Compound nerve action potentials (APs) recorded from the round window membrane were amplified (500

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to 5,000 times), filtered (8 Hz to 8 kHz), averaged (64 observations), and plotted by a Medelec digital averager system. To estimate the auditory function independent of technical problems (displacement of electrodes, etc), Preyer's reflex thresholds were tested with eight different sinusoidal tone bursts between 0.25 and 8 kHz at each session.[26] Vestibular function was tested by recording the vestibulo-ocular reflex and spontaneous nystagmus in the dark. The animals were rotated sinusoidally on a simple platform while the horizontal eye movements were recorded with a Beckman Dynograph recorder. No attempts were made to quantify the responses because of the lack of an established method to calibrate corneoretinal potentials in the guinea pig.

TABLE 1. PROPORTIONAL SCALA MEDIA AREA (MEAN ± SD)

	Cochlear Turns			
	Basal	*Second*	*Third*	*Fourth*
Controls (n = 11)	27 ± 3	36 ± 5	36 ± 4	35 ± 6
Failed obliterations (n = 4)	25 ± 4	36 ± 4	36 ± 4	37 ± 3
Hydropic ears (n = 11)	63 ± 17*	74 ± 15*	68 ± 15*	73 ± 10*

*Differs significantly from controls ($p < .01$, *t* test).

The cochlear and vestibular functions of the hydropic and control ears were tested over 35 to 100 days. Inner ear pressures were recorded as a final experiment. The animals were anesthetized with intramuscular ketamine and xylazine and with intraperitoneal pentobarbital (Nembutal 20 mg/kg). A tracheostomy was performed, and artificial breathing with room air was provided by a Harvard model 66 animal respirator. Hydrostatic pressures in the inner ear fluids were recorded with a servocontrolled micropipet system.[25,29] By an approach through the posterior bulla, a bevelled micropipet (tip diameter, 10 μm) first was placed with a micromanipulator on the round window membrane, where a calibration and baseline determination was performed in a small drop of Ringer's solution. The pipet then was advanced through the round window membrane into the scala tympani, where PLP was recorded, and then through the basilar membrane into the scala media, where ELP was measured. The DC potentials (relative to a silver–silver chloride electrode in the soft tissue of the neck) were recorded simultaneously with the pressure through the micropipet to monitor the location of the micropipet tip. In some of the ears, pressure recordings were complicated by granulation tissue that had formed along the silver electrodes on the round window membrane.

After pressure recording in both ears, the animals were killed painlessly and celloidin-embedded serial sections of the temporal bones were prepared for histologic evaluation of the inner ear. The areas of

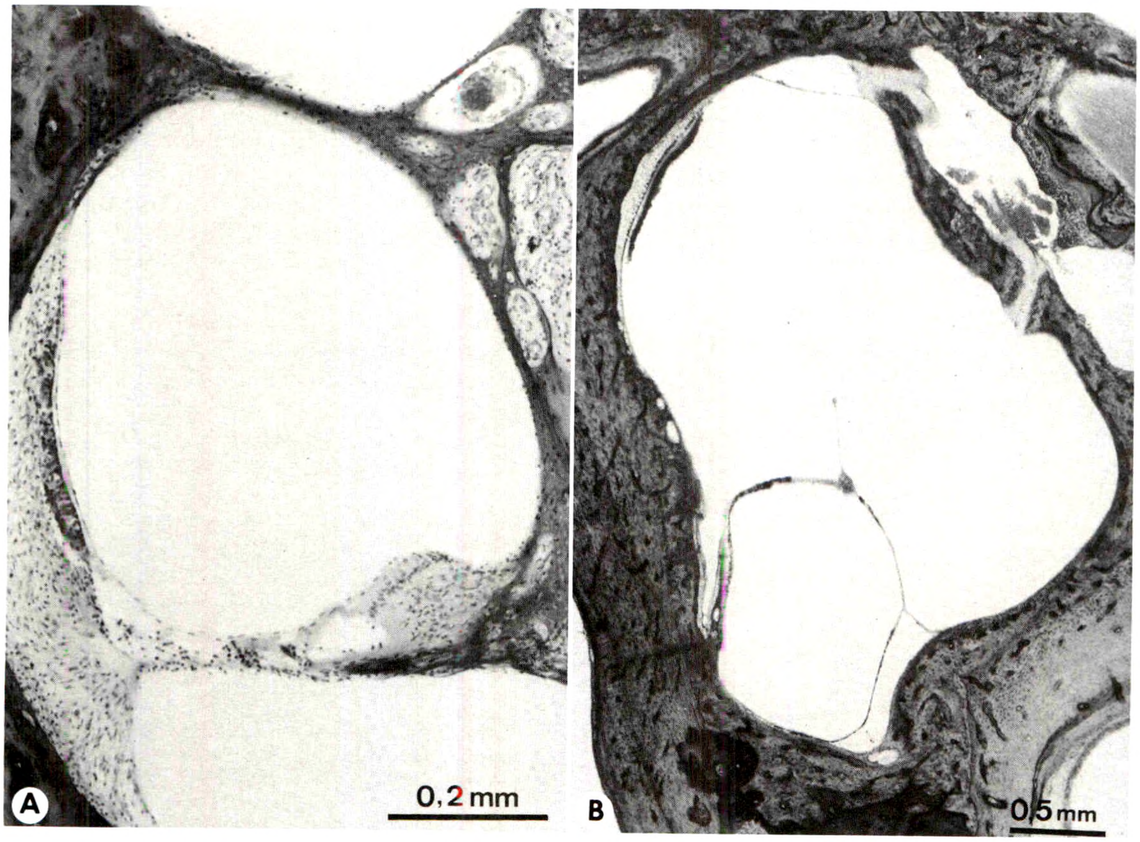


Fig 1. A) Collapsed Reissner's membrane in second turn in guinea pig AX. B) Ruptured saccular membrane in guinea pig AW.

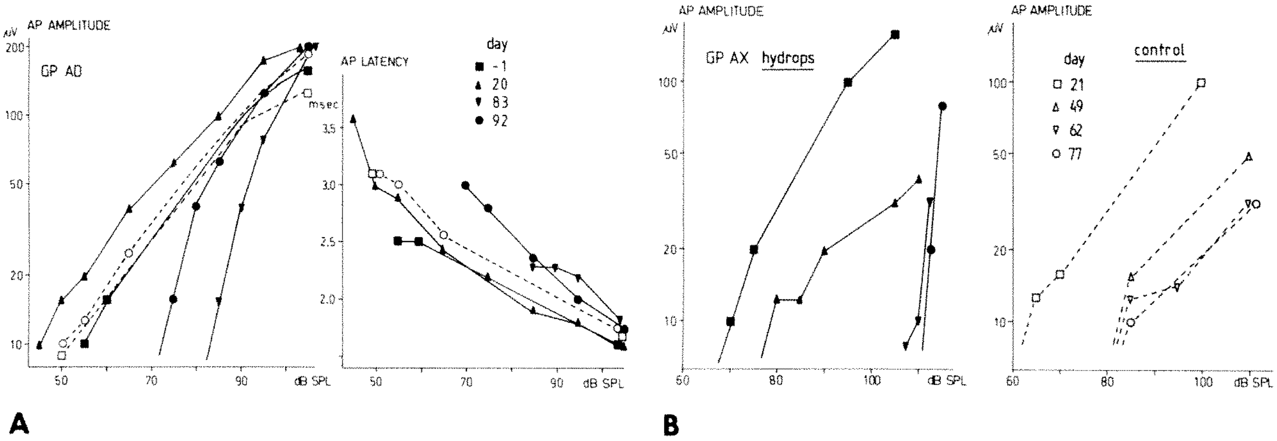


Fig 2. Input-output function of compound action potentials (AP) elicited by 2-kHz tone bursts. Open symbols and broken lines — control ear, solid symbols and solid lines — hydropic ear. A) In guinea pig AD. B) In guinea pig AX, which developed chronic otitis media in both ears. There is shift of input-output curve to right in control ear, and additional inner ear hearing loss with recruitment in hydropic ear.

scala media (SM) and scala vestibuli (SV) of each turn were determined by means of a computerized morphometer (ASBA, Wild and Leitz) and the proportional SM area was calculated as SM/(SM + SV) x 100.

RESULTS

Morphologic Findings. Endolymphatic hydrops was found in 11 of 15 ears (73%) with obliterated endolymphatic sacs (Table 1). Four animals did not develop endolymphatic hydrops; histologic examination of these ears revealed "obliterations" that were not performed deep enough into the endolymphatic duct. These ears will be referred to as failed obliterations. None of the control ears (unoperated ear of the contralateral side) showed hydropic changes. The proportional SM area varied only minimally among control ears and ears with failed obliterations, but was increased significantly in the hydropic ears (Table 1).

In six of 11 hydropic ears Reissner's membrane was distended in all turns. In guinea pig AX, Reissner's membrane was distended in the apical turn, but severely collapsed in the lower part of the cochlea (Fig 1A), including the saccule, while in guinea pig AW, a rupture of the saccular membrane with thickened ends and a collapse of only the lateral part of the basal turn was observed (Fig 1B). In the three other ears, slightly collapsed or wavy Reissner's membranes were seen in single turns.

Cochlear Symptoms. In all 11 hydropic ears, the compound AP thresholds had increased by at least 20 dB with clear recruitment at suprathreshold stimulation (Fig 2A). Preyer's reflex showed a Metz recruitment as illustrated in Fig 3. In some of the control ears, the AP threshold had increased, too, but always without recruitment (Fig 2B, right). This was interpreted as either conductive hearing loss due to slight infections around the electrode and/or as a deterioration of the recording electrode. In the few hydropic ears in which the threshold increased both with and without recruitment (Fig 2B, left) only threshold increases with recruitment were used for further calculations.

The mean threshold increase for 1-, 2-, and 4-kHz tone bursts in all hydropic ears was 36 ± 13 dB (Table 2). The time course of this increase was progressive with slight fluctuations in five ears. In six ears hearing thresholds increased suddenly, 3 weeks (one animal) or 8 to 11 weeks (five animals) after obliteration of the endolymphatic sac. Figure 3 illustrates the time course of hearing deterioration in three animals, each with its corresponding control ear. Action potential threshold increases during

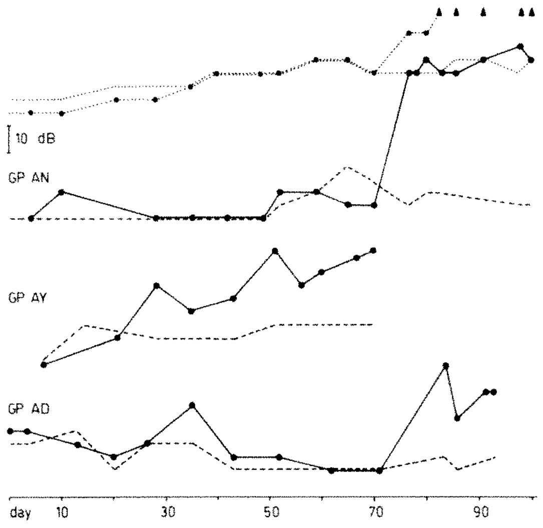


Fig 3. Time course of action potential (AP) threshold increase in three hydropic ears (solid circles and lines) and in corresponding control ears (broken lines). Acoustic stimuli were 2-kHz tone bursts. For guinea pig AN, Preyer's reflex thresholds elicited with 2-kHz tone bursts are also given (dotted lines with solid circles — hydropic ear, dotted line — control ear, triangles — abolished Preyer's reflex). Metz recruitment is seen with Preyer thresholds 40 dB above AP thresholds at beginning, but only 15 to 20 dB higher when AP thresholds increase.

TABLE 2. MEAN ACTION POTENTIAL THRESHOLD INCREASE IN HYDROPIC EARS FOR 1-, 2-, AND 4-KILOHERTZ TONE BURSTS

				Hearing Loss	
Guinea Pig	*Survival Time (d)**	*Total Increase (dB)*	*Increase During Last 2 Weeks (dB)*	*Type*	*Time Course (d)*
BC	35	21	21	P	4-35
AZ	67	42	27	P	29-67
AY	70	26	9	P	21-70
AW	70	43	5	P/S	48-55
BB	71	53	26	P/S	69-70
AT	78	27	10	S	15-25
AO	84	27	28	S	71-77
AD	92	43	21	S	71-83
AX	99	32	0	S	49-56
AN	100	60	12	S	77
AB	100	20	20	S	88-99
Mean ± SD		36 ± 13	15 ± 10		

P — progressive, S — sudden.

*After obliteration of endolymphatic sac.

the last 2 weeks before pressure recording turned out to be the important parameter for correlating cochlear function with inner ear pressure. Therefore, threshold increase during these 2 weeks is given separately in Table 2.

Vestibular Symptoms. An early period of spontaneous nystagmus related to manipulations at the endolymphatic sac had to be distinguished from late episodes of nystagmus related to endolymphatic hydrops (Fig 4).

During the first 2 days after sac obliteration, spontaneous nystagmus toward the operated side was observed in three animals; four animals also showed transient head tilts. Between day 2 and day 7 after the sac obliteration, five of six animals with nystagmus recordings during this period showed spontaneous nystagmus in the dark, with the fast phase toward the unoperated side. These findings disappeared in all animals during the next 2 weeks. All these animals developed endolymphatic hydrops, while none of the animals with failed obliterations showed spontaneous nystagmus.

After 1 month, nine of the 11 guinea pigs with hydrops showed transient episodes of slight spontaneous nystagmus in the dark. In two animals, this could be related to a hearing deterioration in the control ear (acute otitis, fast phase of nystagmus toward the operated ear). Seven of the 11 episodes of spontaneous nystagmus were related in time with hearing deterioration in the hydropic ear (Fig 4, bottom). In three cases the nystagmus was beating toward the hydropic ear, and in four cases toward the control ear. No other late vestibular symptoms such as head tilt or obvious gait instability were observed.

Inner Ear Pressures and Endocochlear Potentials. Figure 5 gives an example of a pressure recording from both the hydropic and the normal contralateral ears in one animal. In control ears, measurements of PLP, ELP, and endocochlear potential (EP) were successful in only four ears. Therefore, additional data from nine normal ears of another study (A. Böhmer, unpublished observations) are included in Table 3. Absolute values of ELP and PLP varied from 1.4 to 4.0 cm H2O among different

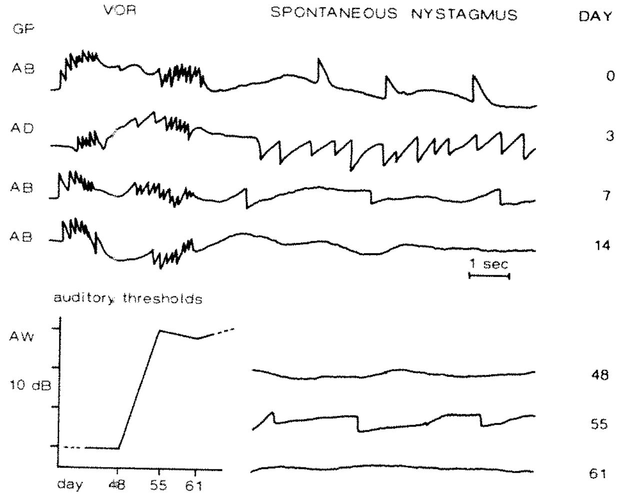


Fig 4. Vestibulo-ocular reflex (VOR) induced by clockwise and counterclockwise horizontal rotation and spontaneous nystagmus in dark related to endolymphatic sac surgery (top four traces) and to auditory threshold increase in hydropic ear (three lower traces). In all traces upward deflections indicate eye movement toward hydropic ear. Topmost recording (day 0) was done 6 hours after obliteration of endolymphatic sac. For guinea pig AW, auditory action potential thresholds (2 kHz) are given at left side. GP — guinea pig.

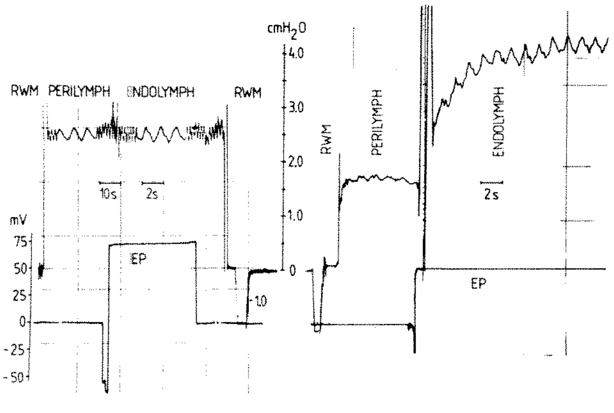


Fig 5. Pressure recording in scala tympani and scala media in control ear (left) and hydropic ear (right) in guinea pig AB 100 days after sac obliteration. Micropipet was guided through round window membrane (RWM) into perilymphatic space (PERILYMPH), and then through basilar membrane into endolymph (ENDOLYMPH). Respiratory pressure oscillations became visible in inner ear fluids, but not on RWM. Direct current potentials recorded simultaneously through micropipet monitored pipet localization: negative potential indicated passing through organ of Corti; positive potential appearing afterward is endocochlear potential (EP), indicating position of micropipet tip in scala media. Before and/or after pressure measurements, calibration (−1.0 cm H2O) was performed on RWM. Note higher endolymphatic than perilymphatic pressure and lowered EP in hydropic ear.

TABLE 3. PERILYMPHATIC AND ENDOLYMPHATIC PRESSURE AND ENDOCOCHLEAR POTENTIALS

	PLP (cm H2O)	*ELP (cm H2O)*	*ELP-PLP Gradient (cm H2O)*	*EP (mV)*
Controls (n = 4)	2.8 ± 0.5	2.8 ± 0.7	0.0 ± 0.1	75 ± 4
Other normal ears (n = 9)	2.1 ± 0.8	2.2 ± 0.9	0.0 ± 0.2	76 ± 4
Failed obliterations (n = 4)	2.8 ± 0.5	2.9 ± 0.8	0.1 ± 0.3	75 ± 4
Hydrops (n = 11)	2.0 ± 1.2	3.2 ± 2.1	1.2 ± 2.4	50 ± 12
Guinea pig				
BC	0.6	1.2	0.6	47
AZ	1.2	1.9	0.7	42
AY	4.4	3.6	−0.8	20
AW	1.8	2.0	0.2	45
BB	2.3	4.0	1.7	55
AT	3.2	3.4	0.2	60
AO	1.0	8.5	7.5	60
AD	1.8	3.8	2.0	63
AX	0.7	1.0	0.3	60
AN	3.5	1.5	−2.0	50
AB	1.5	4.0	2.5	50

PLP — perilymphatic pressure, ELP — endolymphatic pressure, EP — endocochlear potential.

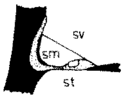
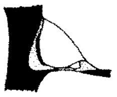
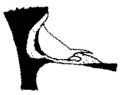
	Auditory threshold increase total	**Auditory threshold increase** last 2 weeks	**Pressure gradient** between endolymph and perilymph	**Morphology**
	dB	dB	cm H_2O	
Group 1 (n = 8)	**5** (0 - 8)	**3** (0 - 8)	**0.1** (-0.4 - 0.5)	
Group 2 (n = 6)	**34** (20 - 53)	**24** (20 - 28)	**2.5** (0.6 - 7.5)	
Group 3 (n = 5)	**38** (26 - 60)	**7** (0 - 12)	**-0.4** (-2.0 - 0.3)	

Fig 6. Endolymphatic-perilymphatic pressure gradients and shape of Reissner's membrane at site of pressure recording in three groups of ears with different patterns of auditory threshold increase. For threshold increases and pressure gradients, mean and (in parenthesis) range are indicated. Sketches of scala media (sm) at pressure-recording site illustrate one typical ear of group. sv — scala vestibuli, st — scala tympani.

control and normal ears, but the pressure difference between endolymph and perilymph (ELP-PLP gradient) in individual ears was minimal, ranging from −0.3 to +0.4 cm H2O. The ears with failed obliterations did not differ from these control ears. The EP measured 70 to 80 mV in all of the control, normal and failed obliteration ears, but was less than 65 mV in all of the hydropic ears.

The mean ELP and PLP in the hydropic ears were in the same range as in the normal ears. Individual hydropic ears, however, showed much larger variations of the ELP-PLP gradient (Table 3).

Correlation Among Hearing Loss, Inner Ear Pressure, and Morphology. Three groups of ears could be distinguished according to the time course of hearing threshold increase. These groups also differed distinctly in the ELP-PLP gradients (Fig 6).

Group 1 showed no significant hearing threshold increase. It included the four control ears and the four failed obliterations. The ELP-PLP gradients were in the same range, −0.4 to +0.5 cm H2O, as in the other normal ears. Temporal bone histology showed normally positioned Reissner's membranes in all these ears.

Group 2 had a hearing threshold increase of more than 20 dB during the last 2 weeks before pressure recording. This group consisted of six hydropic ears in which ELP was higher than PLP (ELP-PLP gradient higher than 0.5 cm H2O). Reissner's membrane was distended in four ears at the pressure-recording site in the basal turn, but partially collapsed in the other two ears.

Group 3 showed a hearing threshold increase of more than 20 dB during the whole observation time (total increase) but no significant further increase during the last 2 weeks before pressure recording. This group included the other five hydropic ears. In none of these ears was ELP significantly increased. The cochlear and vestibular findings of a sudden hearing loss with spontaneous nystagmus 7 weeks after sac obliteration in two of these ears (AX and AW) were in agreement with the histologic findings of ruptures in the membranous labyrinth (Fig 1). Reissner's membrane at the pressure-recording site was wavy in two other ears (AN and AY) of this group and distended in the fifth ear (AT).

DISCUSSION

Our experiments demonstrate equal endolymphatic and perilymphatic hydrostatic pressure in normal guinea pig ears, but important ELP-PLP gradients in ears with experimental endolymphatic hydrops. These pressure gradients were as variable as are auditory threshold alterations in this animal model,[6-8] but were correlated to auditory function: ELP was higher than PLP only in ears with an auditory threshold increase of at least 20 dB during the last 2 weeks prior to pressure recording.

Mean inner ear pressures in three different small series of normal guinea pigs ranged between 2.3 and 6.5 cm H2O, with the higher values obtained when the approach was through the bony cochlea/spiral ligament/stria vascularis instead of the round window membrane/basilar membrane.[20,21,30] Mean PLP and ELP were almost equal in all those series, but none showed ELP-PLP differences for individual ears. Only a few such data are available. Long and Morizono[23] found pressure gradients between −2.2 and +2.7 cm H2O in 25 normal ears, while Ito et al[25] had no gradients larger than 0.3 cm H2O in five ears. The latter finding agrees well with the normal range of ELP-PLP gradients of −0.3 to +0.5 cm H2O found in our animals.

Again, there are only two studies[23,25] that reported ELP-PLP gradients in experimental endolymphatic hydrops. In the latter study, significantly elevated ELP-PLP gradients were measured in five animals with histologically confirmed hydrops 2 to 3 months after obliteration of the endolymphatic sac. Long and Morizono,[23] on the other hand, claimed no difference between ELP and PLP 1 to 25 days after sac obliteration (only two animals were followed longer, and at least one of them had no hydrops).

Direct and indirect experimental evidence reported in the literature suggests a correlation between cochlear function and inner ear pressure.[10-15] However, all the manipulations to change either the PLP or the ELP described in these studies probably did not induce an ELP-PLP gradient, but affected PLP and ELP by the same amount. Reissner's membrane is able to maintain pressure gradients between endolymph and perilymph only when it has lost its high compliance after long-standing distension.[31] Our study demonstrates cochlear dysfunction in relation to a pressure difference between endolymph and perilymph, a condition that has been suspected as a possible cause of hearing impairment in Meniere's disease. However, not all of the different kinds of functional inner ear disturbances that occur in the guinea pig model can be attributed to such ELP-PLP gradients.

In the first weeks after sac obliteration, compound AP thresholds in the low frequency range start to increase and show important fluctuations.[9] In our study these alterations might have been partially missed because of suboptimal recording electrodes resulting in relatively high preoperative hearing thresholds. Important ELP-PLP gradients were never seen within the first 5 weeks after obliteration of the endolymphatic sac.[23,31] These early reversible hearing threshold fluctuations therefore have to be due to another cause.

Also, 2 to 3 months after obliteration of the endolymphatic sac, a positive ELP-PLP gradient occurs in many ears, and this pressure gradient is strictly correlated to mainly irreversible AP threshold increase. Spontaneous nystagmus in this condition is not exactly correlated in time with the hearing loss.

Moreover, in at least two of 11 ears, ruptures of Reissner's membrane or the saccular membrane had occurred, resulting in a sudden hearing loss with recruitment strictly correlated in time with spontaneous nystagmus and in a collapsed Reissner's membrane in the lower cochlea. Endolymphatic pressure was equal to PLP in these two ears. Similar ruptures of the membranous labyrinth together with sudden drops in compound APs also were seen after direct experimental increase of the ELP.[13]

In conclusion, guinea pigs with operatively obliterated endolymphatic ducts develop distension of the endolymphatic space (endolymphatic hydrops) similar to that found in patients with Meniere's disease, and show cochlear and vestibular dysfunction. Endolymphatic pressure is higher than PLP in more than half of the hydropic ears, but not in normal ears. These pressure gradients are correlated to both morphologic and functional changes. Endolymphatic-perilymphatic pressure gradients may contribute to hearing threshold increase, but are not its only cause.

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PERILYMPH FISTULA:
A COMMON CAUSE OF DIZZINESS AND DYSEQUILIBRIUM?

A conference entitled Perilymph Fistula: A Common Cause of Dizziness and Dysequilibrium? will be held Sept 6-8, 1990, in Portland, Oregon. For further information, contact Sharon Newman, Conference Coordinator, Dept of Neuro-otology, Good Samaritan Hospital and Medical Center, 1040 NW Twenty-Second Ave, Portland, OR 97210; (503) 229-7348.

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The XXII Congress of the Pan American Association of Otorhinolaryngology–Head and Neck Surgery will be held December 1-5, 1990, in Buenos Aires, Argentina. For further information, contact Dr Alejandro Terzian, Secretary General, Delfino Turismo SRL, San Martin 427, 1004 Buenos Aires, Argentina; phone 54 1 394-2014/2247/4181, FAX 54 1 111595/54 1 3945379.

Ann Otol Rhinol Laryngol 99:1990

IMBALANCE AND CHRONIC SECRETORY OTITIS MEDIA IN CHILDREN: EFFECT OF MYRINGOTOMY AND INSERTION OF VENTILATION TUBES ON BODY SWAY

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We studied balance in 34 children with chronic secretory otitis media and compared them with 34 age- and sex-matched control children between the ages of 3 and 5 years. In addition to history and examination, objective measurements were obtained by use of a fixed force plate body sway platform in both the control group and the group with chronic secretory otitis media. We took measurements in both groups at an interval of 4 months to ensure that any improvement in body sway could not be attributed to normal maturation. Eight parameters of body sway were compared, including three new parameters not described elsewhere (mean squared velocity, the number of intersections, and velocity moment). Our study showed that balance is significantly worse in children with chronic secretory otitis media compared to a control group. Furthermore, the increased body sway of children with chronic secretory otitis media was returned to the normal range by myringotomy and insertion of ventilation tubes.

KEY WORDS — middle ear ventilation, otitis media with effusion, posturography, vestibular function tests.

INTRODUCTION

Poor balance and clumsiness are not uncommon in preschool children; however, objective assessment by a simple noninvasive method had been lacking[1] until the development of the body sway platform. There is anecdotal evidence that imbalance is improved by myringotomy and insertion of ventilation tubes,[2,3] but an inability to quantify balance has prevented formal assessment.

The objective of this study was to investigate whether there was any difference in body sway criteria between a group with chronic secretory otitis media and an age- and sex-matched control group, and whether myringotomy and insertion of ventilation tubes affected these criteria. We also wished to establish whether a series of related questions and some simple tests of balance were of value in discriminating between normal children and those with chronic secretory otitis media.

METHOD

The control group consisted of volunteers from a nursery school: 17 boys and 17 girls with a mean age of 4.24 years (SD = 0.57). A history was taken with special reference to perinatal problems, developmental milestones, ear infections, and past illnesses. Children with developmental delay, neurologic problems, or chronic secretory otitis media were excluded, but poor balance alone did not constitute a reason for exclusion. Parents were asked whether the child 1) had frequent falls or was clumsy, 2) frequently bumped into objects or misjudged distances, 3) had difficulty climbing or descending stairs, or 4) disliked swings or roundabouts. Middle ear disease was excluded by otoscopy and, when the eardrum could not be visualized, by impedance testing.

The study group consisted of 17 boys and 17 girls with a mean age of 4.27 years (SD = 0.65). They had a clinical diagnosis of chronic secretory otitis media and a history of hearing or speech problems.

The diagnosis of chronic secretory otitis media was made by examination and either tympanometry or pure-tone audiometry or both. As for the control group, children with developmental delay or neurologic problems were excluded.

The group having myringotomy and insertion of ventilation tubes was asked to perform a Romberg test, a Romberg in tandem, and a Fukuda test (stepping on the spot with the eyes closed); the length of time the children could stand on one leg and their ability to hop and kick a ball were noted.

Posturography was performed with a Paedobaroscope force platform (PBS 100/PX) and computed on a Galaxy 2 microcomputer with an analog-to-digital converter and application software.

The force platform measures sway in terms of displacement of the center of pressure from an arithmetic mean position. A rigid frame supports four piezoelectric load cells that fit inside the top of the pedestal frame. The load cells are wired independently to amplifier and conditioner circuits. After amplification, the output signals of the load cells are connected to a 12-bit analog-to-digital converter in the Galaxy microcomputer. The output lines of the analog-to-digital converter are sampled by the computer at 15 Hz, as the maximum frequency to be expected in body sway is less than 5 Hz.[4] We used a fixed force platform because studies have shown that children less than 7.5 years old are

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unable to balance when given conflicting information from visual cues and support surfaces.[5,6]

The subjects were asked to stand on the fixed platform with their feet together over print-marks made on the platform surface and to look at an object on the wall at eye level. This was repeated with the eyes closed, and it was found necessary to give verbal encouragement (counting down from 20 to 0) in order to prevent the children from opening their eyes or becoming distracted. While the instructors knew whether the subject was in the control or the treatment group, they made every effort to give identical instructions under the same conditions. The instructors had no knowledge as to which subjects in the treatment group had effusion present. We had to sacrifice real-time data analysis and display because of the children's short attention span, and for the same reason readings were taken over 20 seconds rather than the usual 60 seconds.[7]

All subjects undergoing myringotomy and insertion of ventilation tubes had body sway measurements in the preceding 24 hours to see if the results could be related to the presence or absence of effusions at operation. Tympanometry was not repeated at this time, so the degree of reduced middle ear pressure cannot be correlated with body sway on the basis of the data we have. Two main types of measurement were used to assess body sway: 1) postural activity, which is related to the overall number of corrective moves needed to keep the body's center of pressure as close as possible to the arithmetic mean position, and 2) postural instability, which relates to the deviation of the center of pressure from the arithmetic mean position.

MEASUREMENTS OF POSTURAL ACTIVITY

Sway Path Length. This is the length, in millimeters per second, of the path circumscribed by the subject's center of pressure for each second of analysis time. It is computed by summating the lengths of the lines joining successive data points and dividing by the analysis time.

$$(1)\qquad \text{Sway Path} = \Sigma\,\begin{matrix} n-1 \\ J=1 \end{matrix}\,([x_{J+1} - xJ]^2 + [J_{J+1} - J_{J+1}]^2)^{1/2}$$

where J = individual points on x/y coordinates.

Velocity of Subject's Center of Pressure. Represented as mean squared velocity (millimeters per second squared), it reflects the energy expended to maintain postural stability.

$$(2)\qquad \text{Mean Squared Velocity} = \Sigma\,\begin{matrix} n-2 \\ J=1 \end{matrix}\,V^2{}_J/n-2$$

Mean Frequency of Oscillation. This is calculated as the frequency (in Hertz) of a circular motion, with the radius of the circle being equal to the mean deflection from the arithmetic mean position and the total length being equal to the sway path.

$$(3)\qquad \text{Mean Frequency} = \frac{\text{Sway Path}}{2\pi \times \text{Mean Deflection}}$$

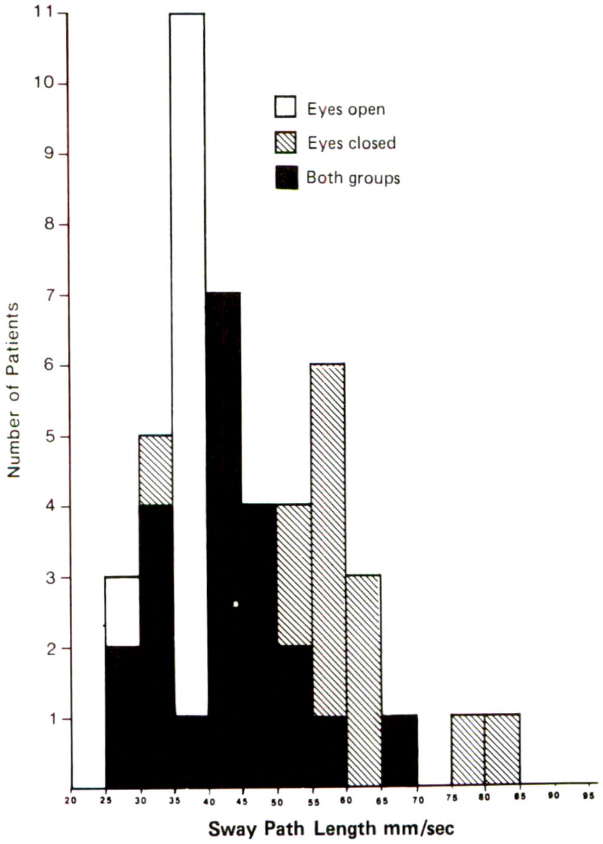

Fig 1. Body sway path length in control group with eyes open and eyes closed.

Number of Intersections. This is the number of times the path of the center of pressure crosses itself. Equations describing the lines joining successive data points were calculated, and a program was devised to analyze the number of intersections.

Velocity Moment. This parameter is a combination of velocity and displacement for the period of analysis.

$$(4)\qquad \text{Velocity Moment} = \Sigma\,\begin{matrix} n-1 \\ J=1 \end{matrix}\,[V_{J+1} \times R_{J+1}]$$

where J = data point and R = displacement.

MEASUREMENTS OF POSTURAL INSTABILITY

Sway Area. This is the total area (in square millimeters) circumscribed by the center of pressure during the period measured.

Displacement of Subject's Center of Pressure. This is presented as mean squared displacement.

Radial Displacement. The displacements are divided into groups so as to plot a histogram of the time spent within a certain distance of the arithmetic mean position. The lateral and sagittal components of each parameter were computed.

The results were compared by means of Student's paired *t* test.

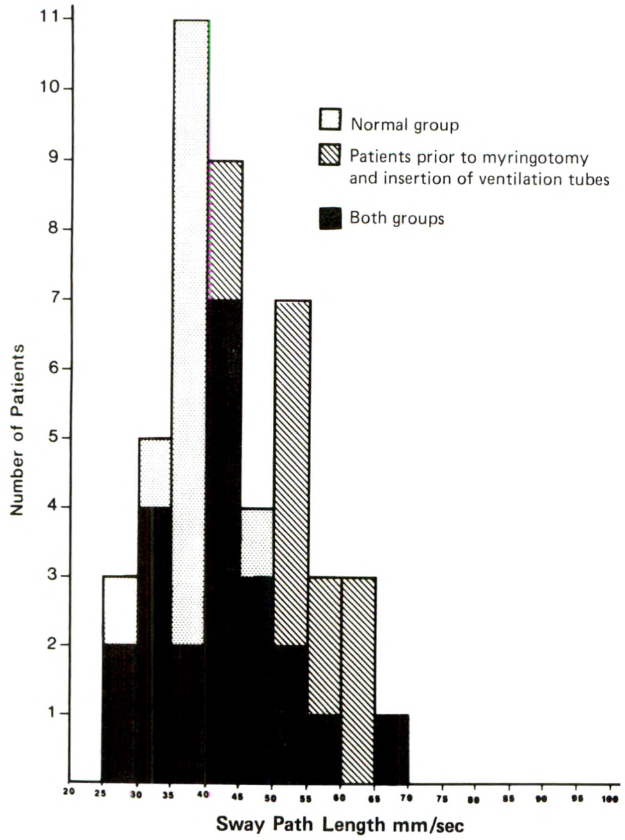

Fig 2. Body sway path length in control group and in treatment group prior to myringotomy and insertion of ventilation tubes (eyes open).

RESULTS

Thirty-four patients underwent myringotomy and insertion of ventilation tubes. At operation 22 had chronic secretory otitis media present; 14 had bilateral effusions, while 8 effusions were unilateral.

A history of clumsiness or unsteadiness was found in 3 of 34 children in the control group and 17 in the study group. However, there was no relationship between those who had a history of imbalance and those whose body sway was greater. Moreover, those whose parents gave a history of improved balance over the time of the study did not consistently show an improvement in body sway. Neither the length of history of chronic secretory otitis media nor the severity of hearing loss at audiometry had any relationship to body sway readings.

Twenty-two children had chronic secretory otitis media verified at operation, and 10 of those had a reported improvement in balance after myringotomy and insertion of ventilation tubes. A further 3 of the 12 without chronic secretory otitis media also had a reported improvement.

There was much variation in the performance tests, particularly in the time a child could stand on one leg. Eleven children in the treatment group had improved in two or more of the clinical tests over the 4 months after myringotomy and insertion of ventilation tubes. However, these were not the same children who had an improvement in body sway measurements.

Body sway measurements were taken in both the control and the treatment groups at an interval of just under 4 months (mean = 3.79 months; SD = 1.5 months). In the control group there was no significant difference between the readings on these two occasions. The measurements varied considerably less within than between the subjects on the two occasions. Body sway measurements were significantly greater with the eyes closed than with the eyes open (Fig 1). Prior to myringotomy and insertion of ventilation tubes the body sway parameters of the treatment group were significantly greater ($p < .05$) than those of the control group (Fig 2), and this difference increases when the subgroup of 22 patients with chronic secretory otitis media found at myringotomy are compared with the control group.

The body sway of the 12 patients who had no chronic secretory otitis media at myringotomy was not significantly different from that of the control group.

Neither the control children nor those who had no chronic secretory otitis media at myringotomy showed any significant alteration of their body sway between the first and second tests.

Four months after the first body sway recording there was no longer any significant difference in body sway between the group who had had chronic secretory otitis media at myringotomy and were treated by insertion of ventilation tubes and the control group after the same time interval, ie, there had been an improvement in body sway in those who had myringotomy and insertion of ventilation tubes such as to bring their body sway into the normal range (Fig 3).

No significant differences in the results were found between the sexes. Body sway measurements did not vary with the nature of the secretions (serous or mucinous), or with whether they were unilateral or bilateral.

DISCUSSION

We found an appreciable difference in body sway between children with chronic secretory otitis media at myringotomy and normal children. Imbalance as quantified by body sway measurements in children with chronic secretory otitis media improved after myringotomy and insertion of ventilation tubes. Children who previously had been diagnosed as having chronic secretory otitis media but who were dry at myringotomy had body sway measurements that were indistinguishable from those of the control group.

History and examination results did not correspond well to body sway measurements. We find this surprising, as the study was inspired by obser-

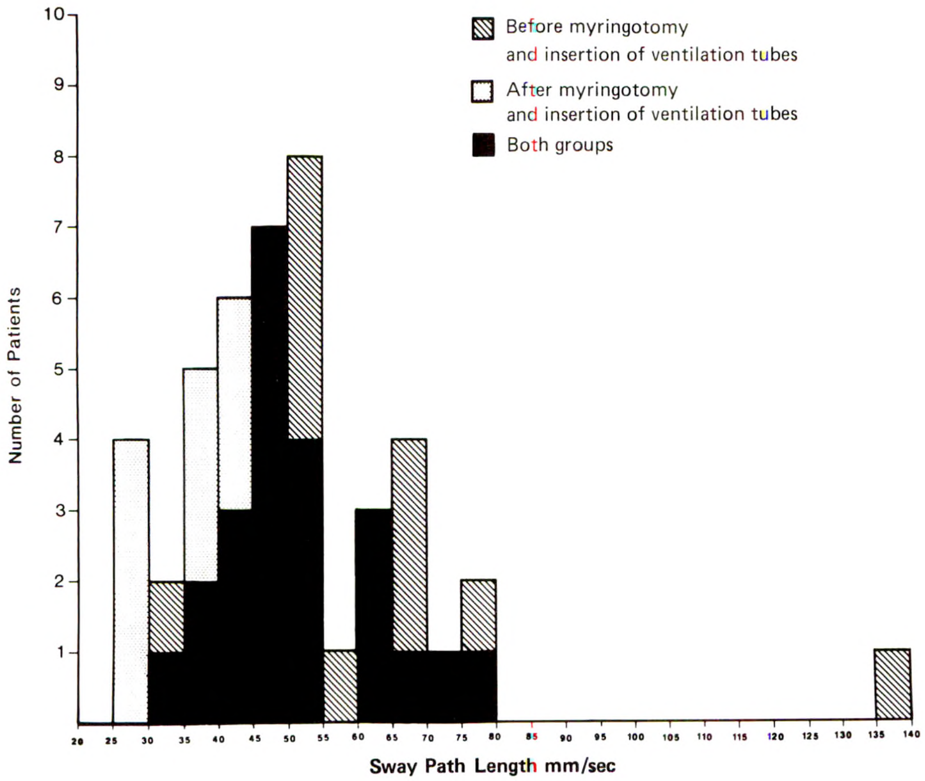

Fig 3. Body sway path length in treatment group before and after myringotomy and insertion of ventilation tubes (eyes closed).

vations made by parents on their children's balance. One explanation is that the history, examination results, and body sway each may be representative of a different aspect of balance. However, the nature of the questioning is likely to have led to an increased incidence in reports of poor balance and its improvement by myringotomy and insertion of ventilation tubes, caused by a desire of some parents to please the questioner. Clinical findings were very variable at this age. (Interobserver error between the clinicians involved was not tested.) In this study body sway appears to be more sensitive and reproducible than clinical examination.

Balance is maintained by three main control systems: visual, vestibular, and ankle-foot proprioception.[8] The loss of information when the eyes are closed therefore produces increased postural activity that is a practical response to the loss of a control loop input.[9-13]

Body sway measurements on a fixed force platform over 20 seconds yield useful information about balance in 3- to 5-year-olds. We achieved surprisingly consistent results, considering the difficulty that might be anticipated in asking children to stand still. Considerable overlap was demonstrated between groups in our study, so that a reliable prediction cannot be made on individual values. However, body sway measurements appear to be useful both in comparing groups and in monitoring changes of balance within an individual or a population. Posturography may have an important research role in young children, whose vestibular function is notoriously difficult to assess.[1,14] These findings support the anecdotal evidence that vestibular function is disturbed in children with chronic secretory otitis media. To date, there is no satisfactory model to explain this finding. A mechanical effect on the round window is possible, although the latter is not in direct contact with the endolymph. The round window is semipermeable,[15] and ionic transfer might alter indirectly the composition of the endolymph via the perilymph. The subsequent changes in ionic channels of the kinocilia and stereocilia might affect not only balance but hearing. Not infrequently, a minor degree of sensorineural high-frequency loss is detected in chronic secretory otitis media, and it is regarded by some as an artifact.

Three new parameters for measuring body sway are described: mean squared velocity, the number of intersections, and velocity moment. The body sway path length was consistently the most useful measurement, in spite of the criticism that it represents a mixture of information derived from other measurements.[16]

CONCLUSION

We conclude that balance as measured by a fixed body sway platform is significantly worse in children between 3 and 5 years of age who have chronic secretory otitis media than in normal children. Furthermore, those differences are abolished by treatment of the chronic secretory otitis media by myringotomy and insertion of ventilation tubes.

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PATTERNS OF EPITHELIAL CELL DEATH DURING EARLY DEVELOPMENT OF THE HUMAN INNER EAR

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A light microscopic study of cell death in a developmental series of otic primordia from 23 human embryos (Carnegie stages 9 to 14) was completed. Degenerated cells were noted predominantly in the placode (stages 9 and 10), cup (stages 11 and 12), and otocyst (stages 13 and 14). A systematic camera lucida study of the appearance and topography of degenerating epithelial cells showed four different areas of cell death in the otic primordia that related to 1) invagination and detachment of the otic anlage, 2) early histogenesis of the statoacoustic ganglion, and 3) development of the endolymphatic duct. The possible role of cell death in the morphogenesis of the inner ear related to morphogenetic movements is discussed.

KEY WORDS — cell death, human embryo, inner ear, morphogenesis.

INTRODUCTION

Embryonic development encompasses not only the process of differentiation and growth but also cell death. Cell death is known to be involved in both normal and pathologic development. A detailed knowledge of the distribution and cytologic characteristics of the areas of embryonic cell death is important for understanding normal and abnormal development.[1-3]

Programmed cell death has been shown to be active in the regression of transient embryonic tissues and in those parts of the embryo undergoing morphogenetic movements such as folding, separation, and confluence of anlagen.[3-9] These morphogenetic movements play a role in the formation of the inner ear of humans and other vertebrates during early development.[10-18]

Areas of cell death have been reported in different primordia of the human embryo[19-22]; however, their occurrence in the epithelial folds of the inner ear has received little attention. We previously have shown that programmed cell death occurs during early morphogenesis of the otic and olfactory plates of chick and mouse embryos.[23-26] The aim of the present work was to study areas of cell death that occur during the early development of the human inner ear and to document their location, morphology, and evolution in order to assess their importance in this developing system.

MATERIALS AND METHODS

This paper is based on the examination of human embryos from the Department of Anatomy and Embryology, Complutense University, Madrid, Spain. The material was classified according to the Carnegie stages devised by O'Rahilly,[17] as summarized in the Table. The age of each embryo was estimated from the developmental stage according to the data of Olivier and Pineau.[27]

HUMAN EMBRYOS USED IN PRESENT STUDY

*Carnegie Stages**	*Human Embryo Designation*	*Pairs of Somites*	*Length (mm)*
9 (2)	GV	3	—
10 (3)	CV-2	6	2.0
	Ca	9	—
	Rm	12	—
11 (3)	CANO	14	—
	OY-6	16	2.4
	Ve-7	20	—
	Be.	20	—
12 (3)	Ce.	24	—
	Ro	26	3.0
	FAUS-5	27	4.0
	C-1	30	—
13 (3)	GV-3	—	4.5
	Pt-13	—	4.8
	DO-1	—	4.9
	JD-1	—	5.0
	JD-2	—	5.3
	Pt-8	—	5.0
14 (3)	OY-4	—	6.0
	GV-5	—	7.0
	Mu-3	—	6.4
	VG	—	7.0
	DO-2	—	7.0

Parentheses indicate number of otic primordia studied for obtaining cell counts.

*Devised by O'Rahilly.[17]

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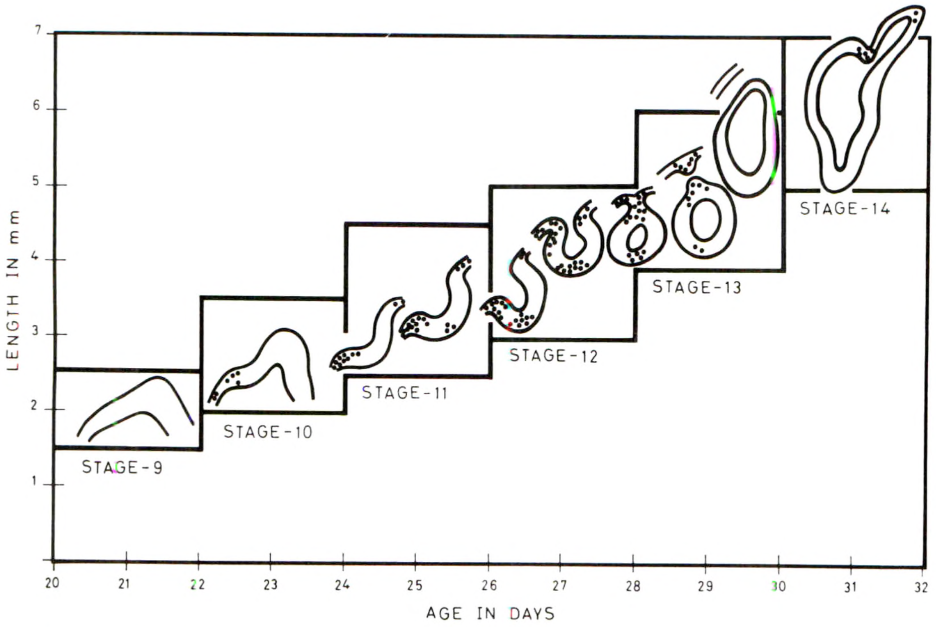

Fig 1. Schematic drawings taken from cross sections of otic primordia in human embryos. Black dots show location of dead cells and phagocytes. Age in postovulatory days is plotted on abscissa and embryonic length in millimeters on ordinate. Rectangles indicate Carnegie stages. (Drawings are not to scale.)

Twenty-three human embryos (Carnegie stages 9 to 14) were studied. The embryos were sectioned and stained for light microscopy. Seventeen specimens were stained with hematoxylin and eosin and the remaining six specimens with Mallory's or van Gieson's stain. Necrotic cells were observed under oil immersion with a 100/1.32 objective microscope and were identified on the basis of nuclear morphology using the criteria described by Glucksmann.[1] Serial sections of otic primordia were drawn with use of a camera lucida at x25, and the sites of cell degeneration were marked. Degenerating cells were counted in all sections. Serial and total counts of pyknotic figures of each stage are represented as averages of three otic primordia of different embryos, except for stage 9, in which both otic primordia were studied from the same embryo. Although no corrections were made to allow for splitting of degeneration sites between adjacent sections, the numbers obtained were comparable among different embryos.

RESULTS

Early development of the human inner ear can be divided into stages based on the shape of the otic primordium. Initially, cephalic ectoderm forms a placode; subsequent invagination gives rise to a cup that closes, detaches from the surface, and forms a cyst. This simple pear-shaped otocyst in later development will be expanded into the membranous labyrinth. The studies reported here reveal that intense necrotic activity takes place during the developmental period extending from the placode stage to the otocyst stage of inner ear development. The pattern and number of necrotic sites throughout this period of otic morphogenesis are summarized in Fig 1.

Otic Placode (Stage 9). The otic primordium of the stage 9 embryo is represented by a thickening of the cephalic ectoderm adjacent to the hindbrain, which has become a three- or four-layered pseudostratified epithelium. The otic invagination has not yet developed. Cell degeneration is limited to a few pyknotic figures (18 ± 5 necrotic cells per rudiment) that are localized randomly in the border between the otic epithelium and the marginal cephalic ectoderm (Fig 2A).

Early Otic Cup (Stages 10 and 11). The area of programmed cell death is detected in the otic epithelium at the beginning of its invagination (stage 10) as a single zone of cellular necrosis (97 ± 22 necrotic cells per rudiment) located at the edge of the lateral and caudal folds of the invaginating otic cup; medial and cranial portions remain free of cell degeneration.

The appearance of the otic anlage at the beginning of stage 11 (Fig 2B) is similar to that of stage 10. The distribution and number of degenerating cells (119 ± 29 necrotic cells per primordium) have not changed significantly, and the otic epithelium maintains a steady rate of programmed cell death. Concurrently, several mitotic figures are present, homogeneously scattered around the lumen of the otic epithelium (data not shown).

Late Otic Cup (Stages 11 and 12). During the end of stage 11 and most of stage 12, further invagination of the otic primordium transforms the cup into a vesicle. This vesicle remains open until the end of stage 12 and maintains communication with the exterior (amniotic cavity) through the otic pore.

There is a second and significant change in the morphology of the otic rudiment during stages 11 and 12. Some of the epithelial cells of the ventral wall of the cup migrate across the basement membrane into the underlying ventral periotic mesenchyme and give rise to the primordium of the stato-

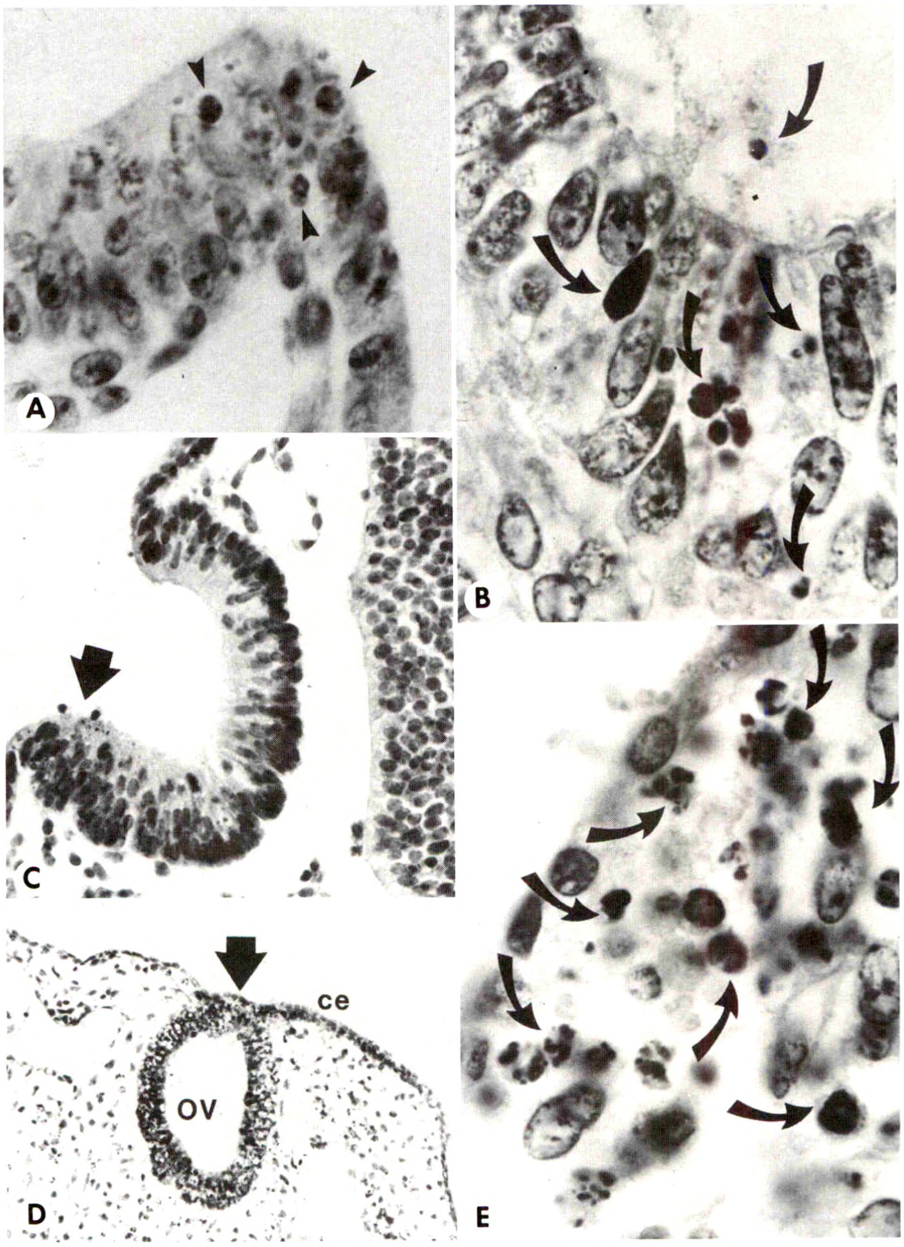

Fig 2. A) Micrograph of frontal section through external edge of otic placode in later stage 9 embryo (H & E, original x400). Few degenerating cells are present at border (arrowheads) between otic epithelium and cephalic ectoderm. B) Transverse section of stage II embryo through anterior portion of external edge of otic cup (H & E, original x1,000). Some degenerating cells and associated cellular debris (arrows) are present in epithelial layer. C) Transverse section through otic cup of human embryo at stage 12 (Mallory's stain, original x160). Arrow shows location of programmed cell death in otic primordia at this developmental stage. D) Low-power view of stage 12 otocyst (ov) that appears closed but remains connected to cephalic ectoderm (ce) (H & E, original x100). E) Higher-power view of otocyst shown in D (H & E, original x1,000). Note many dead or dying cells (arrows) located in zone of fusion and closure.

acoustic ganglion. While this is occurring in the region of the otic epithelium, where cells of this epithelium are migrating away to form the eighth sensory cranial ganglion, the thickness of the epithelium increases considerably, the cells are clearly disorganized, and the basal lamina seems to be discontinuous (Fig 3D). At the same time several mitotic figures can be seen among ganglionic and otic cells.

Cellular degeneration in this later cup stage is localized in two distinct areas.

The first zone (which started during the previous stage) is in the lateral and caudal folds of the otic cup (Fig 2C), where it forms an extensive area of cell death (190 ± 37 pyknotic sites per otic cup) at the end of stage 11. By stage 12 this region of necrosis encircles the otic pore (243 ± 34 pyknotic sites per otic cup).

The second zone of cell death is limited to the ventral otic epithelium overlying the area of the developing primordium of the statoacoustic ganglion. This new locus of cell death, the ventral otic cup pyknotic zone, makes its first appearance at the end of stage 11 (57 ± 14 pyknotic sites per otic cup) as a single wave of degeneration that increases considerably during stage 12 (141 ± 32 pyknotic sites per primordium) and continues as a band of pyknotic cells in the most ventral wall of the otic cup and in the statoacoustic ganglion primordium, where cellular degeneration is scattered.

Early Otocyst (Stages 12 and 13). During the end of stage 12, growth of the otic walls brings the edges of the otic pore into close apposition and eventually they fuse. But the newly closed otocyst remains connected to the surface ectoderm via a small epithelial stalk (Fig 2D). At stage 13 the insertion of the otic

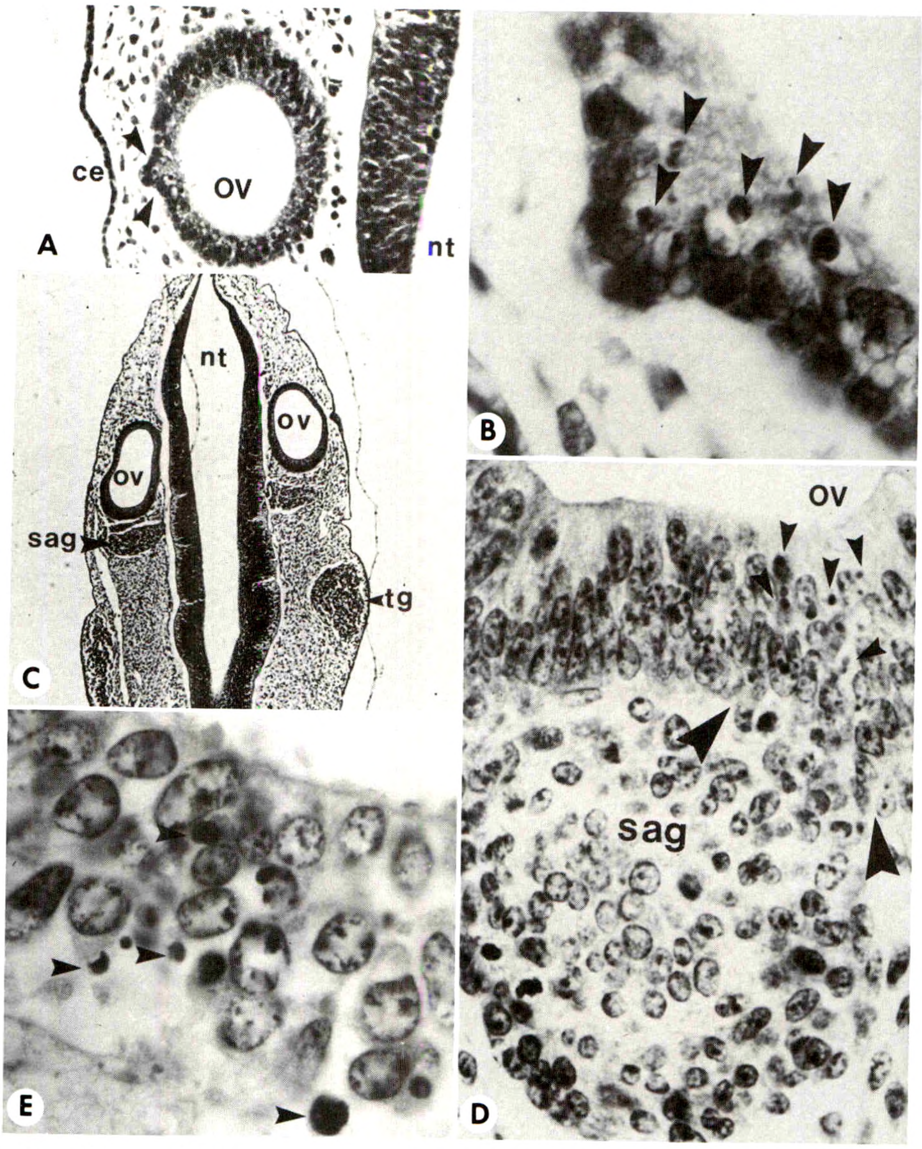

Fig 3. A) Low-power view of stage 13 otocyst (ov) already detached from cephalic ectoderm (ce) and appearing embedded in cephalic mesenchyme close to neural tube (nt) (Mallory's stain, original x100). Note zone on lateral wall of otocyst displaying remains of connecting stalk (between arrowheads). B) Higher-power view of remains of connecting stalk in A (Mallory's stain, original x1,000). Arrowheads — dead cells at closure point and connecting stalk of otocyst. C) Frontal section through otocysts at early otic vesicle stage (stages 12 and 13) showing morphology of periotic head region during this period (H & E, original x25). nt — neural tube, ov — otocyst, sag — statoacoustic ganglion, tg — trigeminal ganglion. D) Higher magnification of ventral wall of otocyst (ov) and statoacoustic ganglion (sag) at stage 12 (H & E, original x250). Cell degeneration and epithelial disorganization are found in this region of otocyst's wall. E) Higher-power view of wall of otocyst at stage 12 (H & E, original x1,000). Note number of dead or dying cells (arrowheads) located in ventral epithelium of otocyst next to otic ganglion.

stalk on the otocyst is interrupted as this vesicle finally detaches from the cephalic ectoderm and becomes a closed cyst surrounded by cephalic mesenchyme (Fig 3A). Histologic sections reveal the otocyst to be a simple pear-shaped vesicle with significant differences in the thickness of its walls. The dorsal portion of the otocyst thins into a simple cuboidal epithelium, while the ventral portion remains multilayered. The statoacoustic ganglion has already formed (Fig 3C).

At stage 12, the closure of the otic pore is accompanied by cell death. A wide necrotic area appears in this zone of epithelial fusion (286 ± 64 pyknotic cells per otocyst), overlapping and extending the cell death area in the otic folds that accompanied the process of invagination during the previous stages. At the present stage, most necrotic cells appear to be located in the epithelial stalk, the adjacent cephalic ectoderm, and the superficial otic epithelium (Fig 2D,E). Some dying cells were also found in the space between the ectoderm and the epithelium of the otocyst's wall.

Just after the otocyst has detached from the cephalic ectoderm (stage 13), the necrotic area is similar to that found in the preceding stage (Fig 3A,B), in which all degeneration sites are concentrated at the vicinity of the closing point in the otic epithelial wall, in the cephalic ectoderm (245 ± 67 pyknotic cells per otocyst), or in between these two epithelia. By the end of stage 13 the amount of cellular necrosis is notably reduced (88 ± 33) in the above-mentioned locations, and by stage 14 the amount of pyknosis at these sites is insignificant.

The ventral pyknotic zone follows a similar time course during these early otocyst stages. It intensifies while the statoacoustic ganglion is forming and reaches its maximum (187 ± 26) by the end of stage 12 (Fig 3D,E). Pyknosis then diminishes along this ventral wall (74 ± 26 pyknotic cells per otocyst), and by the end of stage 13 no cellular degeneration is detected in the ventral wall of the otocyst.

Late Otocyst (Stages 13 and 14). From the end of stage 13 onward, a complex series of epithelial

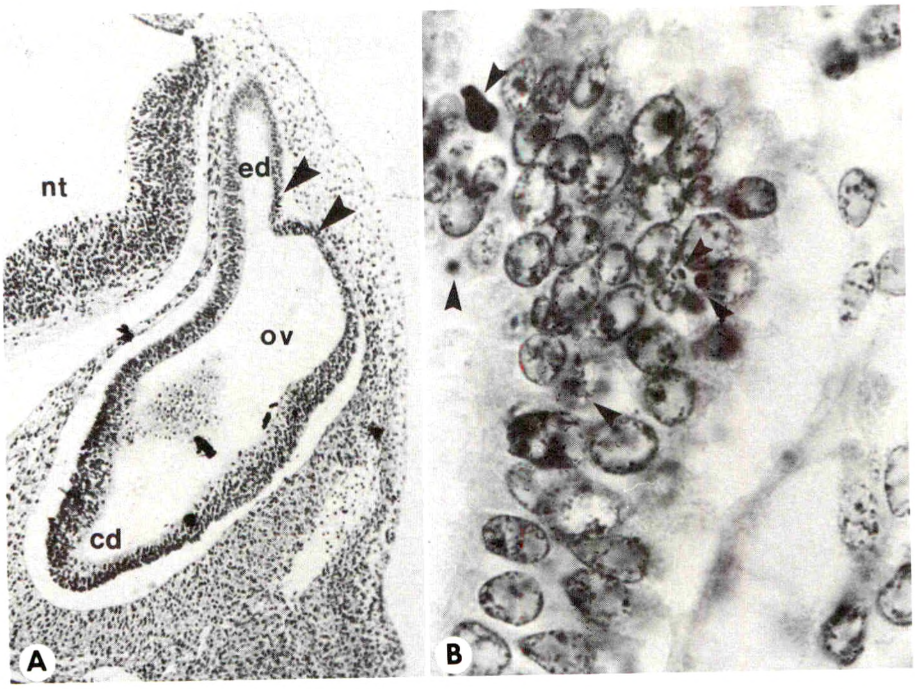

Fig 4. A) Micrograph of right otocyst (ov) of stage 14 embryo (H & E, original x100). Emerging endolymphatic duct (ed) is observed in form of invagination of dorsal wall. Zone between arrowheads (Anson's fold) displays normally occurring cellular degeneration. nt — neural tube, cd — cochlear duct. B) Higher-power view of Anson's fold shows localization of dead and dying cells (arrowheads) (H & E, original x1,000).

movements begins to transform the otocyst into the intricate structure of the mature membranous labyrinth. By the end of stage 13 or at the beginning of stage 14, the otocyst has begun its morphogenesis. From the medial-dorsal face of the otocyst a hollow tube, the endolymphatic duct, has grown out as a prolongation of the otic cavity. In the middle of stage 14 this endolymphatic duct has elongated and projects dorsally (Fig 4A). At this developmental stage an epithelial fold (Anson's fold) can be distinguished that serves as a marker to define the insertion of the lateral aspect of the endolymphatic duct on the dorsal wall of the otocyst (Fig 4A). At the site of Anson's fold a small band of cell death is observed (48 ± 11 necrotic sites per otocyst) that surrounds the insertion of the endolymphatic appendage from the outer (early stage 14) to the inner walls (later stage 14) of the endolymphatic duct (Fig 4B).

At the end of stage 14 the rudiments of the semicircular canals and the coiled cochlear tube start to bulge out from the otocyst. In all these remaining portions of the otic epithelium we found no pyknotic cells.

DISCUSSION

In the human embryo, programmed cell death takes place during the formation of the otocyst. Cell death seems to be a constant feature in this early development of the otic primordium. Programmed cell death shows a typical morphologic pattern in all embryos at the same stage and seems to relate to invagination and detachment of the otic anlage, early histogenesis of the statoacoustic ganglion, and growth of the endolymphatic duct. Our findings suggest four distinct temporospatial patterns of cell death during early development of the inner ear (Fig 1).

An early phase extends from the time of otic placode formation (stage 9) to the period of placodal folding (stages 10 and 11). During this developmental period, necrotic cells and cellular debris are found aggregated at the edges of the otic placode simultaneously with the formation of the otic folds. The present investigation in the human inner ear thus confirms the observation that cell death is present during and correlates with bending of several ectodermal rudiments such as the optic placodes during the formation of the lens[6] or the neural plate.[10] The role of cell death during these morphogenetic movements remains mostly a matter of conjecture. Our observations suggest that cell death occurs simultaneously with invagination movements and proliferative activity in the otic epithelium, which has been shown in the rat and other mammals to have a higher mitotic index than cephalic ectoderm. The loss of a number of cells in restricted areas of rapidly growing tissue may have profound effects on its morphologic development, permitting lateral cell displacement into adjoining regions and therefore leading to the process of folding.[3,10] Furthermore, examination of the degeneration pattern in the embryonic human inner ear reveals that pyknotic cells are concentrated in those portions of the otic primordium in which invagination is more pronounced.

Cell death at the edges of the otic placode may be interpreted as morphogenetic degeneration, according to the terminology of Saunders and Fallon,[5] that might be involved in the invagination and folding of the otic placode and play a mechanical role as has been described for the formation of several embryonic primordia. Nevertheless, as has been reported for these other primordia, other mechanisms are concurrently involved in the invagination of the otic placode, including interactions with the extracellular matrix or the action of cytoplasmic structures within the otic epithelial cells — for instance, contraction of an apical terminal bar network of microfilaments.[28]

At stages 12 and 13, a new area of cell death appears during the closure of the otic vesicle by fusion of the epithelial cells that form the otic pore and during its detachment from the cephalic ectoderm. This area of cell degeneration seems to be required to obliterate the lumen of the otic pore and to separate the otocyst from the surface ectoderm. Previous reports have already associated cell death with the process of epithelial fusion. Localized cell degeneration has been shown to be present during closure of the neural tube,[29,30] during fusion of both the palatal shelves[16] and facial prominences,[18] and in detachment of the lens from the surface ectoderm of the head. Previous work[31] reported localized cell degeneration in the connecting stalk of the otocyst of the rat embryo and suggested that detachment of the otic primordium from the cephalic ectoderm occurs via genetically controlled cell death. Our results in the human embryo are in agreement with such a hypothesis.

In summary, the morphogenesis of the human inner ear between stages 9 and 12 progresses through a complicated but orderly maze of linked epithelial cell movements. Cell death, invagination, vesicle formation, and ectodermal separation appear to be associated in a temporal and spatial relationship. Qualitatively, these results resemble those described for other embryonic anlagen, suggesting that programmed cell death in the developing inner ear may play a similar role.

There is a third area of cell degeneration that occurs throughout the period of the statoacoustic ganglion formation (stages 11 and 13). This area of cell death is found in the medial-ventral wall of the otocyst overlying the developing statoacoustic ganglion.

An in vitro fate map of the mouse otocyst[32] showed that the medial-ventral wall of the otic vesicle gives rise to the neuroblasts of the statoacoustic ganglion. The neurons that compose this cranial ganglion in the chick embryo have been shown to be primarily of placodal origin, with a minimal contribution of neural crest cells forming a few vestibular neurons.[33,34] Furthermore, the times of terminal mitosis documented for these otocyst-derived neurons and the time of greatest cell division activity in the otic epithelium[34,35] coincide with the period of cell degeneration in the ventral-medial wall of the otocyst. Therefore, the third cell death area observed in the ventral otic epithelium might represent histogenetic degeneration[36] related to neuroblast proliferation, migration, and differentiation in the formation of the statoacoustic ganglion. Perhaps some of the cells remaining in the ventral wall of the otocyst lack trophic signals for migration and differentiation and consequently degenerate, forming the ventral pyknotic zone of the otic primordium.

The role of cell death in neuronal development has been chiefly considered in terms of target-dependent cell degeneration.[37-39] Since our results have documented the presence of degenerating cells at a time well before axonal or dendritic outgrowth and synaptic junctions occur in the developing inner ear,[40] this causal relationship can be excluded in the present case.

Finally, the fourth area of cell death described here corresponds to the development of the endolymphatic duct and sac anlage from the dorsal wall of the otocyst. It previously has been shown in other vertebrates that the growth of the endolymphatic primordia takes place by cellular reorganization rather than proliferation and that there is a low mitotic activity in the endolymphatic wall, while proliferation is increased in the rest of the otic epithelium.[18,25,26] The degenerating and necrotic cells in the endolymphatic duct next to Anson's fold may represent a barrier between two cell populations that are known to have different mitotic patterns.[25,26,41]

The fact that no cell degeneration could be found in the early developing semicircular canals or cochlear duct suggests that cell death does not participate in their formation at this early developmental period of human inner ear organogenesis. However, it might be possible that cell death is present at older stages in the above-mentioned locations, as has been reported in rat embryo inner ears.[31]

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OSTEOGENIC SARCOMA OF THE FRONTAL SINUS

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Occurrence of osteogenic sarcoma in the craniofacial bones is limited. The case presented here is only the second reported case of osteogenic sarcoma of the frontal sinus, occurring in an 80-year-old woman who presented with proptosis and developed neurologic symptoms. The radiographic appearance was of a diffuse opacity with thickening of the calvaria. Tumor tissue was adherent to the dura, and there was a fairly good initial response with the methotrexate sodium–cisplatin combination chemotherapy used, but the outcome was fatal.

KEY WORDS — frontal sinus, osteogenic sarcoma.

INTRODUCTION

Osteogenic sarcomas, irrespective of their location, form about 40% of all bone tumors. Although the site of predilection for osteogenic sarcoma is at the metaphyses of long bones, in large series those of the head and neck, usually the mandible or maxilla, make up to 10% of all osteosarcomas.[1] Osteosarcomas of the extragnathic craniofacial bones, those bones of the skull except the jaw bones, constitute less than 2% of all.[2] Reports in the literature include at least one case each of the ethmoid,[3] occiput,[4] frontal bone,[5] and frontal sinus.[6] The purpose of this report is to introduce to the literature only the second reported case of osteosarcoma of the frontal sinus.

CASE REPORT

An 80-year-old woman presented in February 1985 with a progressive swelling of 6 weeks' duration over the left side of the forehead (Fig 1).

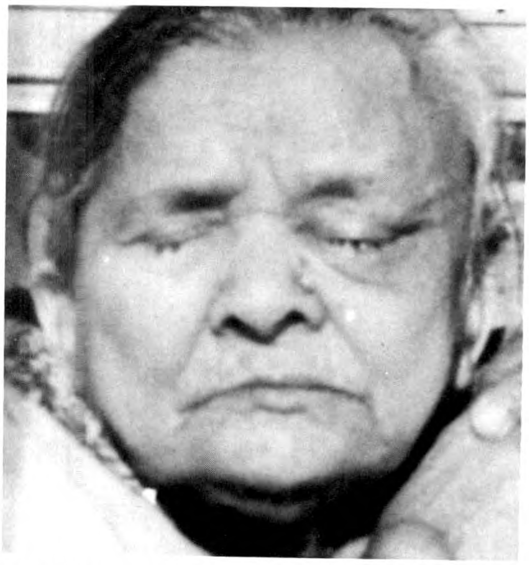

Fig 1. Photograph of patient showing swelling in left frontal region.

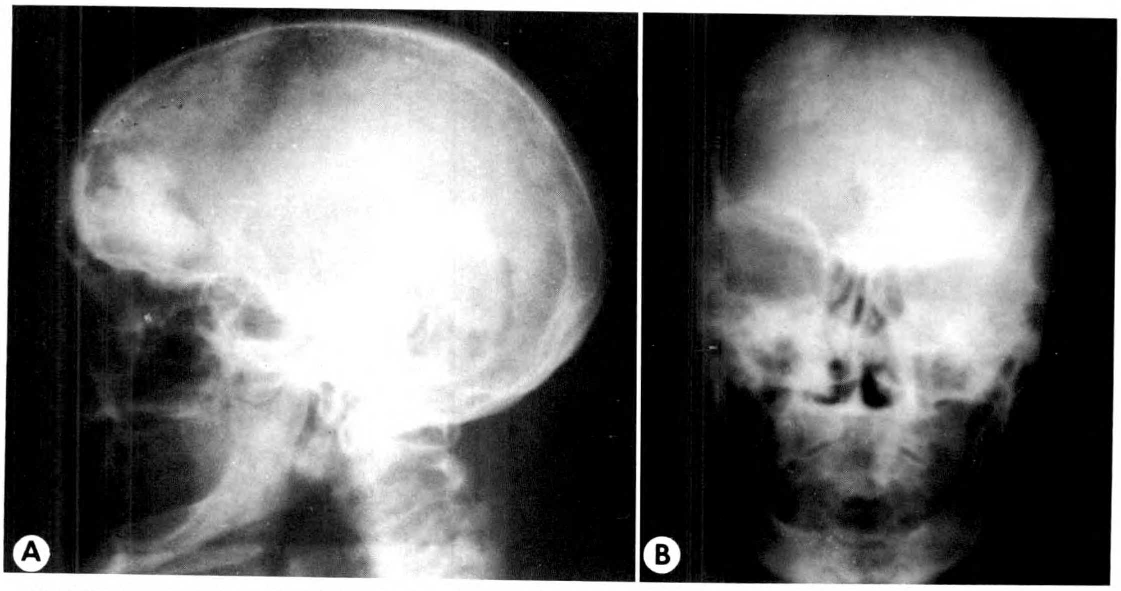

Fig 2. Radiographs of skull. A) Lateral view, showing diffuse opacity in left frontal sinus with thickening of outer table. B) Anteroposterior view, showing mass in left frontal sinus.

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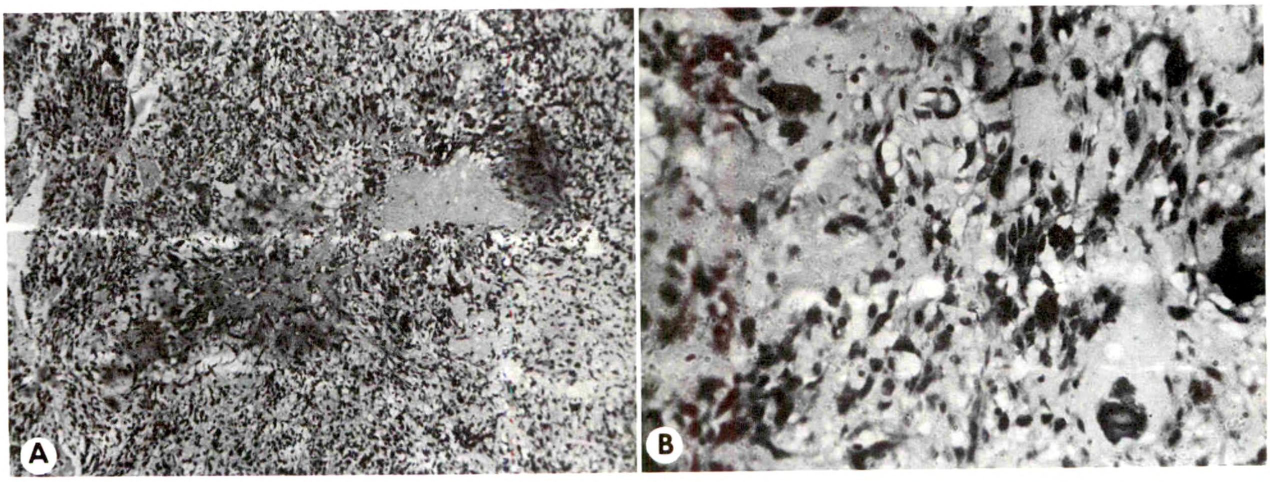

Fig 3. Photomicrographs showing osteoid tissue (H & E, original x100). A) With foci of calcification. Malignant osteoblasts are seen lining newly formed osteoid. B) Surrounded by malignant osteoblasts. Sarcomatous stroma contains few tumor giant cells.

Severe, continuous frontal headache with progressive impairment of vision in the left eye had been present for 3 months. No history suggestive of increased intracranial tension, bone-ache, or fracture anywhere in the body was present. Past history was unrevealing. Pertinent physical findings were limited to the left eye and left frontal region. There was a bony, hard, tender swelling of about 13 x 6 cm over the left frontal region. Fullness above the left eye was evident to palpation, but the superior orbital rim was intact. Severe chemosis was present, with proptosis of about 6 mm, and the patient was unable to open her left eye. Ocular movements and pupillary reflexes were intact. Findings on fundoscopy were normal.

Results of admitting laboratory studies, including serum calcium and serum enzyme studies, were within normal limits. Radiographs of the chest showed normal findings, and so did those of the long bones. A skull radiograph showed a dense opacity extending inward from the left frontal bone and filling the frontal sinus (Fig 2). With a preoperative diagnosis of a primary malignant tumor of the frontal sinus, surgery was undertaken after a week. As soon as a muscle flap was elevated in the left frontal region, a friable, unencapsulated, grey and gritty mass that bled on touch was encountered filling the whole of the frontal sinus. The frontal dura was exposed in places, and the tumor tissue was tightly adherent to it. Most of the tumor tissue except that intimately sticking to the dura was removed.

The histopathologic report termed the tumor an osteogenic sarcoma (Fig 3). Meanwhile, from the fifth day postoperatively the patient became increasingly disoriented, with abnormal behavior and loss of memory. A curative resection was precluded in view of the patient's age and the location and nature of the neoplasm. Chemotherapy consisting of methotrexate sodium 100 mg intravenously weekly and cisplatin 50 mg intravenous infusion was started on the ninth day postoperatively. Considerable improvement in the condition of the patient occurred within 7 days of starting chemotherapy, when the patient became calm and started to recognize people. However, the outcome was fatal, as the patient suffered a massive myocardial infarction on the 12th day of chemotherapy.

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EFFECT OF ARACHIDONIC ACID ON THE INNER EAR BLOOD FLOW MEASURED WITH A LASER DOPPLER FLOWMETER

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The present study was undertaken to clarify the effect of arachidonic acid (AA) on the inner ear blood flow of rats as measured with a laser Doppler flowmeter. With the rats under anesthesia with sodium pentobarbital, the middle ear was approached ventrally and a laser Doppler probe was positioned over the lateral wall of the cochlea. Drugs were administered via the subclavicular artery. The dose range of each drug was determined so as not to affect the systemic blood pressure. The AA (20 to 70 μg) increased the inner ear blood flow dose-dependently; this effect was abolished by indomethacin (5 mg orally). Both prostaglandin E2 (PGE2; 1 to 50 ng) and CS-570, a PGI2 analogue (12.8 to 25.6 ng) caused a dose-dependent increase in the inner ear blood flow. The response of PGI2 was shorter than that of PGE2. On the other hand, a stable thromboxane A2 (STA2; 30 to 80 ng) decreased the inner ear blood flow dose-dependently. Administration of PGF2α (0.2 to 3 μg) showed no effect on the inner ear blood flow. These results indicated that the effect of AA was mediated mainly via PGI2 and PGE2.

KEY WORDS — arachidonic acid, cochlear microcirculation.

INTRODUCTION

Disorders of the inner ear blood flow may result in a variety of clinical symptoms, such as sudden sensorineural hearing loss[1] and sudden onset of vertigo.[2] Many approaches have been utilized to examine the inner ear blood flow in animal models: 1) direct observation of flow in vivo,[3,4] 2) histologic studies,[1,2] 3) electric impedance plethysmography,[5-7] 4) the microsphere technique,[8-10] and 5) the laser Doppler flowmeter.[11,12] The laser Doppler flowmeter, introduced by Cummins et al,[13] is an acceptable method for measuring blood flow through the superficial area of many tissues, and it recently has been applied to the inner ear blood flow. In the cochlea it has been demonstrated that there is a good correlation between the results obtained with a laser Doppler flowmeter and those obtained with the microsphere technique[14] or direct observation.[12] Compared with these procedures, a laser Doppler flowmeter provides an acceptable measurement of the inner ear blood flow.

Metabolites of arachidonic acid (AA) are well known to regulate peripheral circulation. Arachidonic acid was metabolized to prostaglandins (PGs) and to thromboxane (TX) by cyclooxygenase, and to leukotrienes (LTs) by lipooxygenase. Recently, the synthesis of PGs in the inner ear was demonstrated in guinea pigs,[15,16] suggesting that the inner ear circulation also may be regulated by PGs. Indeed, treatment by aspirin, which inhibits cyclooxygenase, causes disorders of the inner ear circulation. Also, the synthesis of PGs was found to be increased by auditory stimulation. However, the effect of AA or PGs on the inner ear circulation has never been examined.

The purpose of the present study is to examine the effect of exogenous AA and PGs on the inner ear blood flow of rats as measured by a laser Doppler flowmeter.

MATERIALS AND METHODS

Principle of Laser Doppler Flowmeter. The laser Doppler flowmeter (ALF 2100, Advance, Japan) in our study uses a helium-neon laser. The laser output beam is transmitted to the measurement probe via a quartz optical fiber. An He-Ne laser produces a monochromatic light source (632.8 nm) that is reflected well by RBCs. Light reflected by stationary media has the same frequency as the emitted light, while light reflected by moving media (RBCs and any other moving particles) is shifted in frequency according to the Doppler principle. It provides a voltage output that is proportional to the product of the number of particles within the measurement volume (approximately 1 mm^3 in skin) and the velocity of those particles, ie, blood flow. This laser Doppler flow value represents the volumetric flow of RBCs in the tissues (ie, the product of number density of moving cells, their mean volume, and their root-mean-square velocity). The laser Doppler value is linearly proportional to blood flow as confirmed by other blood flow measurement techniques, including xenon clearance,[17] the microsphere technique,[18] and plethysmography.[19]

Operative Procedures. Thirty Wistar rats, weighing 250 to 300 g, were used. All rats were confirmed to have a normal Preyer's reflex before experiments. The animals were anesthetized with sodium pentobarbital (50 mg/kg, intraperitoneally). One percent

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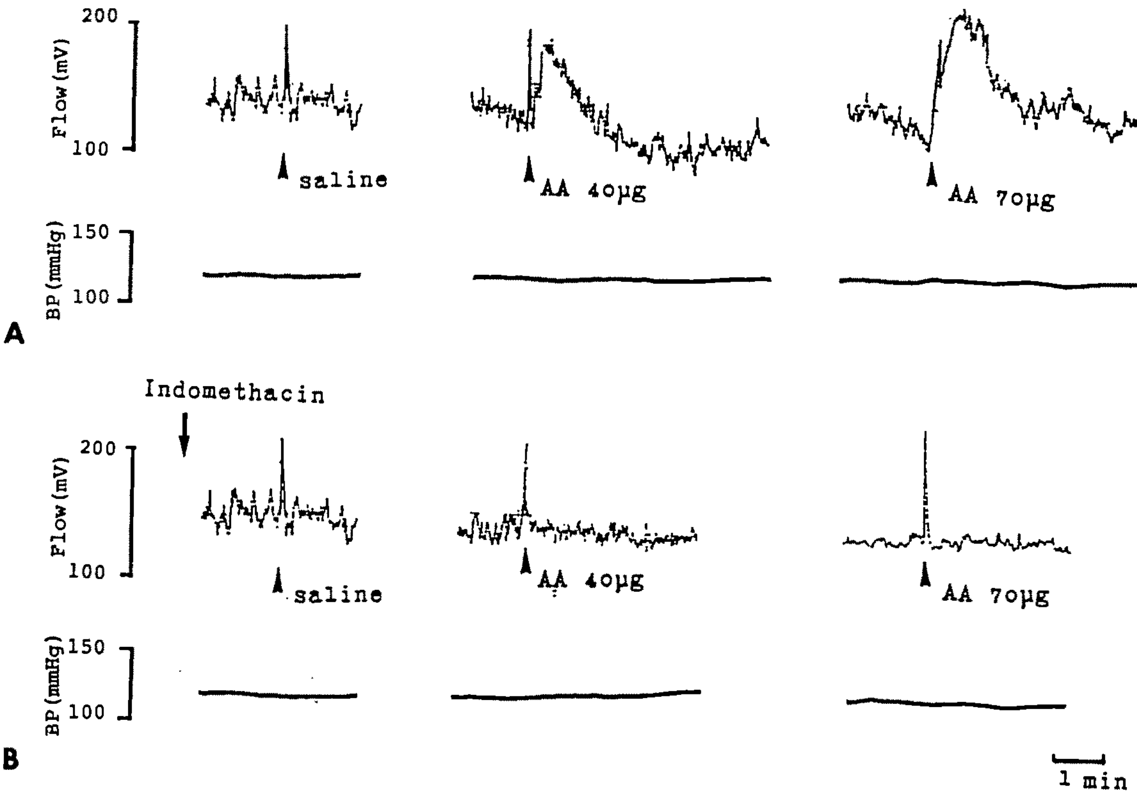

Fig 1. Typical records of effect of arachidonic acid (AA) on inner ear blood flow when administered via subclavicular artery. Arrowheads — administration of saline and AA, respectively; BP — blood pressure. A) Response to AA (40 and 70 μg). B) Response to AA 1 hour after treatment with indomethacin (5 mg, orally).

lidocaine was given subcutaneously where skin incisions were placed. After the tracheotomy the animals were ventilated artificially with a respirator (Harvard 683). Each animal's head was rigidly fixed with a nontraumatic headholder (Narishige). A catheter was placed in the femoral artery and connected to a pressure transducer (Nihon-Kohden, MPU-05, RP-5). Another catheter for drug administration was inserted at the subclavicular artery and guided to the vertebral artery. The location of the catheter was verified with angiography. Body temperature was maintained at 37°C with a heating pad. The middle ears were approached ventrally and the bulla was opened without disturbing the ossicles or tympanic membrane, and the middle ear was judged normal by direct visualization. A laser Doppler probe (ALF 2100 Advance, Japan; diameter, 1 mm) was positioned on the basal turn of the cochlea after the overlying mucosa was removed with cotton pledgets. The blood flow and systemic blood pressure were recorded on a multi-pen recorder (Rikaden, R-16).

Experimental Procedures. The following drugs were used: sodium arachidonate (Sigma) 20 to 70 μg; PGE2 (Sigma) 1 to 50 ng; PGF2α (Sigma) 0.2 to 3 μg; CS-570, a stable PGI2 analogue (Sankyo), 12.8 to 25.6 ng; and 9,11-epithio-11,12-methano-TXA2 (STA2), a stable TXA2 analogue (Ono), 30 to 80 ng. The pH range was between 7 and 8 in all drug solutions. The dosage of each drug was determined so as not to affect systemic blood pressure.

After an equilibration period of 20 minutes, each drug was injected intra-arterially in a volume of 100 μL. Dose-response curves were performed noncumulatively every 20 minutes to allow a sufficient interval for blood flow to return to the baseline before additional injections. Blood flow of 218 ± 12 mV and blood pressure of 116.6 ± 5.1 mm Hg were measured for all animals at the start of the experiments. Preliminarily, it was confirmed that a good reproduction of each drug response could be obtained for 2 hours after starting the experiments. Experimental values are presented as percent change from the baseline. All data are expressed as mean ± SEM.

RESULTS

Arachidonic Acid. Figure 1 presents typical records of the inner ear blood flow that occurred when AA was administered via the subclavicular artery. Arachidonic acid caused a dose-dependent increase in the inner ear blood flow, without changing systemic blood pressure. The response to AA lasted for approximately 2 minutes and was abolished 1 hour after treatment with indomethacin (5 mg, orally) (Fig 1). The dose-response curve for the effect of AA is shown in Fig 2A. On the other hand, the inner ear

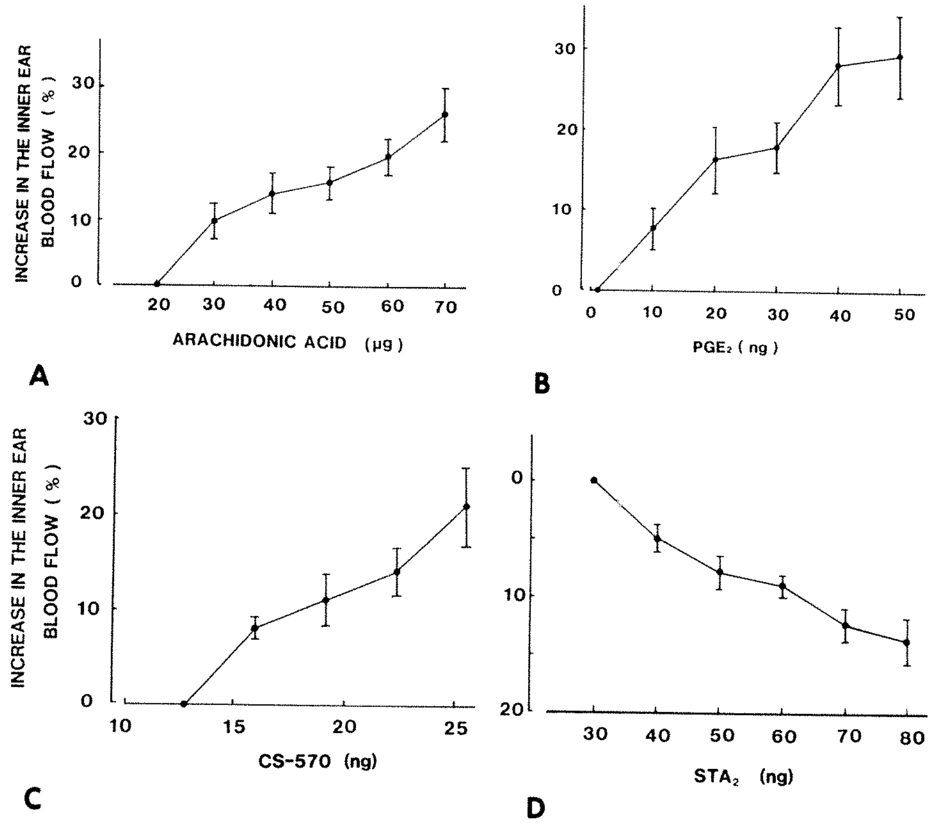

Fig 2. Effect of experimental agents on inner ear blood flow when administered via subclavicular artery. Values are presented as percent change from baseline. A) Arachidonic acid. Each point represents mean ± SEM for seven animals. B) PGE2. Each point represents mean ± SEM for five animals. C) CS-570. Each point represents mean ± SEM for five animals. D) STA2. Each point represents mean ± SEM for five animals.

blood flow and blood pressure did not change when AA was administered via the femoral vein in the same dose range.

PGE2, PGI2, PGF2α, and TXA2. Figure 3 shows typical records of the effects of PGE2, CS-570, STA2, and PGF2α on the inner ear blood flow. PGE2 and CS-570 increased the inner ear blood flow as much as AA did. The response to PGE2 continued for approximately 2 minutes, while that to CS-570 continued for 0.5 to 1 minute. PGE2 and CS-570 caused the increase in the inner ear blood flow dose-dependently in a dose range of 1 to 50 ng and 12.8 to 25.6 ng, respectively (Fig 2B,C). On the other hand, STA2 (30 to 80 ng) decreased the inner ear blood flow dose-dependently (Fig 2D). PGF2α had no effect on the inner ear blood flow in a dose range from 0.2 to 3 μg, in which blood pressure did not change. At more than 3 μg, PGF2α caused an increase in systemic blood pressure followed by an increase in the inner ear blood flow.

DISCUSSION

Escoubet et al[15] and Tran Ba Huy et al[16] reported that PGs were synthesized in the vascular structures of the cochlea (stria vascularis and spiral ligament) in guinea pigs in vitro. According to these authors, the main PGs synthesized in the lateral wall were PGI2 and PGF2α, but PGE2 was also present in lower quantity. When exogenous AA was added in the incubation medium, PGE2 synthesis was increased greatly (1,020%). PGE2 and PGI2 usually have a potent vasodilating effect. From these findings, it was considered that the homeostasis of the inner ear microcirculation was regulated by a subtle balance of their respective secretions. However, the effect of PGs on the inner ear blood flow has never been examined in detail. Until now, the inner ear blood flow of rats has never been measured with a laser Doppler flowmeter. In this study we could measure the inner ear blood flow of rats, which has experimental implications because we can make various experimental models using rats.

We administered AA or PGs via the subclavicular artery in order to estimate the direct influence on the inner ear. We used the drugs in a dose range that did not affect systemic blood pressure. Arachidonic acid increased the inner ear blood flow of rats dose-dependently. Once released, AA is metabolized rapidly to PGs by cyclooxygenase and to LTs by lipooxygenase. Indomethacin, which inhibits cyclooxygenase, abolished the response to AA. This indicated that the response to AA was mediated by cyclooxygenase products (PGs) and not by lipooxygenase products (LTs). This suggestion was supported

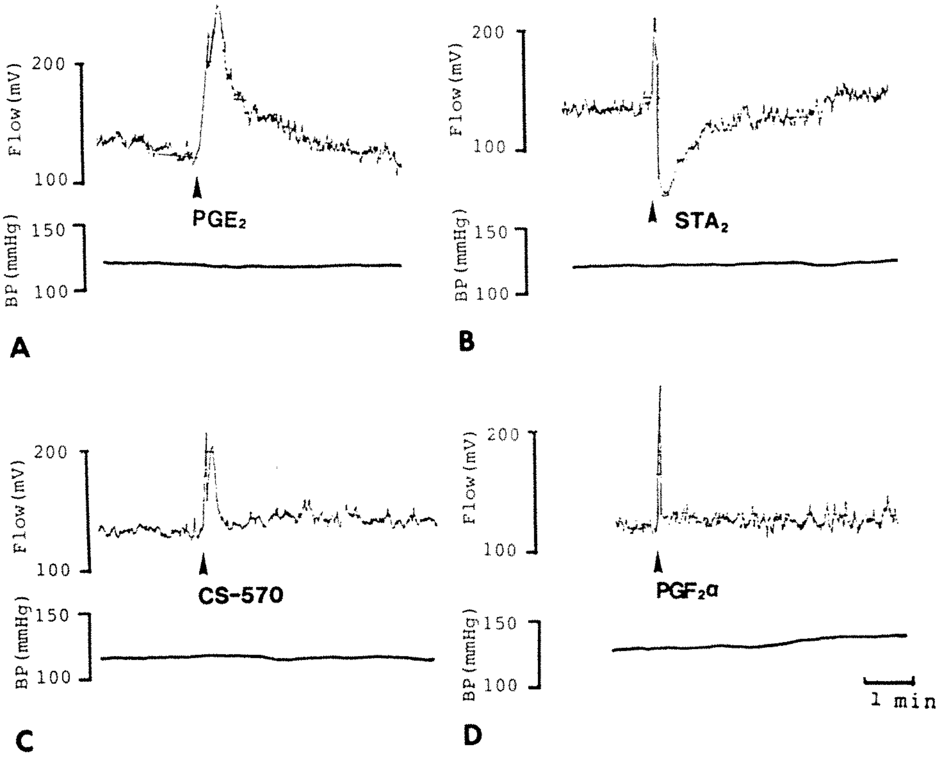

Fig 3. Typical records of effect of experimental agents on inner ear blood flow. Arrowheads — administration of agent via subclavicular artery; BP — blood pressure. A) PGE2 at 40 ng. B) STA2 at 60 ng. C) CS-570 at 22.4 ng. D) PGF2α at 2.0 μg.

by the finding of Tran Ba Huy et al[16] that LTC4 was not detected in the lateral wall even when AA was added. PGE2 and PGI2 also increased the inner ear blood flow as much as AA did. The response to CS-570, a PGI2 analogue, was shorter than that to PGE2 or AA, and the response to PGE2 resembled that to AA. On the other hand, PGF2α, another main metabolite of AA in the cochlea,[16] showed no effect on the inner ear blood flow. The reason for the lack of direct PGF2α effect on the inner ear blood flow is unclear. One possibility is that the receptor for PGF2α is absent in the inner ear vasculature. From these results, we considered that the increase in the inner ear blood flow induced by AA may be mediated mainly through PGE2 rather than PGI2. STA2, an analogue of TXA2 that is a potent vasoconstrictor, decreased the inner ear blood flow dose-dependently. Tran Ba Huy et al,[16] however, found little TXA2 in a medium incubated with the lateral wall of cochlea, regardless of whether exogenous AA was added. Therefore, TXA2 seems not to participate in the response to AA. The existence, however, of TXA2 receptors in the inner ear vessels was demonstrated, because exogenous TXA2 caused a decrease in the inner ear blood flow. It is possible that TXA2 may play a role in the disturbance of the inner ear microcirculation in some conditions such as sudden sensorineural hearing loss and sudden onset of vertigo.

To summarize, AA, CS-570, and PGE2 increased the inner ear blood flow, whereas STA2 decreased it. PGF2α had no effect on it. The response to AA may be mediated via PGE2 and PGI2. Regulation of inner ear blood flow by AA and its metabolites is suggested.

ACKNOWLEDGMENTS — We are indebted to Ono Pharmaceutical Co, Ltd, and Sankyo Co, Ltd, for supplying 9,11-epithio-11,12-methano-TXA2 and CS-570, respectively.

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JEJUNAL INTERPOSITION FOR REPAIR OF STRICTURE OR FISTULA AFTER LARYNGECTOMY

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Complications following total laryngectomy may include pharyngocutaneous fistula or pharyngeal stricture. Traditional techniques of repair of fistula and stricture with local or regional flaps lead to a high rate of failure. In this study, we report 18 patients treated by secondary jejunal interposition (JI) to rehabilitate swallowing following recalcitrant postlaryngectomy stricture or fistula. All patients had undergone total laryngectomy with or without partial pharyngectomy for treatment of squamous cell carcinoma of the larynx (8) or hypopharynx (10). Four were stage II; 5, stage III; and 9, stage IV. Thirteen patients (72%) regained swallowing function. Complications of secondary JI included perioperative death (2), flap loss (1), and persistent fistulas (3). Jejunal interposition may be the best modality in the rehabilitation of swallowing in patients with persistent fistula or stricture that fails to respond to traditional management.

KEY WORDS — fistula, jejunal interposition, laryngectomy, stricture.

Pharyngocutaneous fistula and hypopharyngeal stricture after total laryngectomy with or without partial pharyngectomy are common problems. Most fistulas close primarily and most strictures respond to dilation. However, repair of major fistulas and strictures unresponsive to conservative treatment may require major surgical intervention.

The incidence of fistula and stricture has been reported by many authors.[1-5] A better understanding of the cause of these complications has led to a decline in their incidence. The surgical management of fistula and stricture has evolved as new methods of reconstruction have been introduced.

This report looks at the use of free tissue transfer (jejunal interposition [JI]) for the treatment of those fistulas and strictures that were most severe and did not respond to traditional treatment of these complications. Complications and outcome are reported.

MATERIALS AND METHODS

The medical records of patients who underwent pharyngectomy and JI after laryngectomy were reviewed. Data were obtained by reviewing hospital charts, operative notes, staging diagrams, pathology reports, and otolaryngology clinic records. Only patients who were treated for a postlaryngectomy fistula or stricture were included. Specifically, patients in whom JI was used for primary reconstruction after tumor ablation were excluded, as were secondary procedures in which recurrent tumor was found.

RESULTS

The entrance requirement for this study was the presence of a pharyngocutaneous fistula or severe stricture following total laryngectomy. Of the 18 patients studied, 9 patients had a pharyngocutaneous fistula, and another 9 had a severe stricture (Table 1). There were 12 men and 6 women, divided equally between the two groups. The average age was 65 years in both groups. Twelve patients (66%) had received radiotherapy following the laryngectomy.

The initial surgical procedure in all patients was total laryngectomy. Partial pharyngectomy was included in 10 of the 18 patients. Two patients had bilateral neck dissections and 11 had a unilateral neck dissection as indicated at the time of total laryngectomy. Five patients had no neck dissection performed.

Nine patients had a persistent fistula at the time of JI. Four of those nine patients had undergone prior attempts at surgical repair with local or regional flaps to close the fistula. Two of these four patients underwent two procedures, failing both. Five patients with fistula had a nearly circumferential hypopharyngeal defect and were closed with JI as their first attempt of closure (Table 2).

Nine other patients had strictures at the time of their JI. Four of these strictures occurred in patients in whom a fistula was treated conservatively and allowed to heal by secondary intention. Two of these four patients had nearly complete stenosis of the hypopharynx and could not be dilated. The other seven patients were dilated one to nine times (average, 4.5 times each). The end point of attempts to dilate was the inability to pass a dilator. Three patients underwent further attempts to rehabilitate

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Presented at the meeting of the American Laryngological Association, San Francisco, California, April 1-2, 1989.

TABLE 1. TUMOR CHARACTERISTICS

	Stricture	Fistula
Site		
Hypopharynx	8	2
Larynx	1	7
Stage		
II	0	4
III	4	1
IV	5	4

TABLE 2. PRIOR TREATMENT OF COMPLICATIONS

	Fistula	Stricture
None	2	5
Local flaps	2* (1x and 5x)	2 (1x and 2x)
Pectoralis major myocutaneous flap	1*	1†
Deltopectoral flap	—	2
Dilation	7 (1x and 9x)	—

*These patients also underwent dilation.

†This patient failed local flaps twice.

swallowing, including local flaps in two patients (one and five times each), and a pectoralis major myocutaneous flap on a third patient. All of these efforts resulted in persistent strictures.

All patients underwent completion of their pharyngectomy in order to prepare for JI. Defects extended from the tongue base to the thoracic inlet.

End-to-end arterial anastomoses were performed in all but one case. The recipient artery was the external carotid artery in seven cases, superior thyroid artery in four cases, ascending pharyngeal and facial artery in two cases each, and the transverse cervical, lingual, and occipital arteries in one case each. Venous anastomosis to the facial vein was performed seven times; to the internal jugular vein, five times; to the external jugular vein, four times; and to the transverse cervical vein twice.

Bowel ischemia time ranged from 1 hour to 4 hours. The average ischemia time was 2 hours 30 minutes. All proximal pharyngojejunal anastomoses were hand sewn. A stapling device was used in eight of the jejunoesophageal closures. The others were hand sewn.

Thirteen of the 18 patients regained swallowing function after JI in an average of 9.7 days (range, 7 to 30 days). This includes four patients who developed a fistula following JI that healed without further intervention. Five patients never regained an intact alimentary tract. This group included two patients who died during their hospitalization from respiratory complications. Two other patients died, 3 and 4 months after JI, one of respiratory failure and the other of a newly discovered liver cancer. These patients had persistent fistula but no evidence of squamous cell carcinoma. The one surviving patient in this group still uses a nasogastric tube for nutrition after two unsuccessful attempts to surgically close a fistula following JI.

Four patients had clinical and radiographic evidence of minor stricture after JI. These strictures were successfully managed by dilation. All these patients are maintaining their weight with an oral diet.

Three patients had postoperative vascular complications. One patient awoke from anesthesia with a cerebrovascular accident on the same side as the microvascular anastomosis. The arterial anastomosis was to the transverse cervical artery. Another patient had a postoperative fistula leading to breakdown of the arterial microvascular anastomosis 1 month after JI. A third patient had bleeding from the neck 3 months after being successfully rehabilitated with JI. Ligation of the external carotid artery to control bleeding resulted in loss of the JI. The hypopharynx was subsequently reconstructed with a second JI. The external carotid artery was the recipient artery in both of these cases.

Two patients had minor complications that did not prolong their hospitalization. One patient had gastrointestinal bleeding requiring transfusion. Another patient had an abdominal wall hematoma leading to wound dehiscence, which healed with local wound care.

All patients have been followed for at least 7 months. Seven patients are alive with no evidence of disease, with follow-up ranging from 7 to 73 months; six of these patients have had no evidence of disease for greater than 2 years. Three patients treated for stricture died of recurrent carcinoma 3 to 25 months after JI. Seven patients, including the four with persistent fistula, died of other causes 1 to 10 months after JI. One patient is alive with inoperable neck recurrence 7 months after JI.

DISCUSSION

The use of the JI in patients with benign stricture or fistula has been described as part of many series.[6-8] In these series, either the use of JI for repair of complications is used infrequently or such cases are not separated from the patients undergoing primary repair after surgical ablation.

Prior to the introduction of the deltopectoral flap, fistulas were managed by primary closure, skin graft, and the use of local flaps. These methods often failed, especially in patients who had received prior irradiation.[9] With the use of the deltopectoral flap, large fistulas could be closed, but required multiple stages.[10]

One-stage reconstruction of fistula is possible with the pectoralis major myocutaneous flap. The thickness of the flap is a limitation, especially for hypopharyngeal reconstruction.[11] The flap is difficult to fold for a circumferential defect and its bulk may occlude the tracheostoma.

Hypopharyngeal stricture after laryngectomy with or without partial pharyngectomy is not uncommon.[4,5] This complication is most often managed by serial dilation.[12] When the stricture cannot be dilated, further operative intervention is indicated. Pectoralis myocutaneous flap reconstruction is an option, but again the bulk of the flap over the tracheostoma is a hazard. Two other flaps, an axial island cheek flap[13] and a tongue base flap, have been described.[14] These reports indicate good success in selected cases.

Although most fistulas and strictures after laryngectomy respond to traditional methods of rehabilitation, some of these problems persist. These patients are left with nasogastric or gastric feeding tubes, salivary incontinence, or open neck wounds. They become discouraged after failure of traditional methods and often become depressed and withdraw from society. In some cases the need for prolonged hospitalization stresses and tests the financial capabilities of the hospital. Jejunal interposition provides an option for these frustrating and seemingly unsolvable complications. Although our success rate (restoration of swallowing) of 72% seems low, this must be considered in the context of the severity of the problem. No other option is available to solve some of these difficult cases. Perioperative mortality and morbidity (namely, fistula and vascular complications) are obvious and significant considerations. Other alternatives include free flaps, stomach and colon, all of which carry significant comorbidity and potential for complications. Microvascular expertise, available in an increasing number of centers, makes JI a consideration for repair of these laryngectomy complications.

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The 17th annual meeting of the American Auditory Society will be held November 15, 1990, in Seattle, Washington. For further information, contact Robert A. Dobie, MD, Chair, AAS Program Committee, Otolaryngology-Head and Neck Surgery, University of Washington RL-30, Seattle, WA 98195.

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IMAGING CASE STUDY OF THE MONTH

OSSIFIED AURICLE IN ADDISON'S DISEASE

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CASE REPORT

A 46-year-old man was admitted to the otolaryngology department for treatment of chronic otitis media of several months' duration. The patient gave a history of having suffered from tuberculosis that was successfully treated over 17 years before. The patient was known to be suffering from Addison's disease for over 12 years and had been receiving substitutional therapy in the form of 7.5 mg of prednisone daily. On examination, a right tympanic perforation with purulent discharge was noted. The auricles of both ears were rock-hard and could be moved forward as a single unit only. There were no signs of inflammation or scarring on the auricles, and they were not sensitive to palpation. No other pathologic findings were noted. The patient was successfully treated for his otitis media. Further evaluation of the state of his ears was done by radiography and computed tomography.

IMAGING FINDINGS

An anterior-posterior film demonstrated bilateral symmetric ossification of both auricles with a trabecular pattern that could be observed at their lower third (Fig 1).

An axial computed tomographic scan revealed marked ossification of both auricles (Fig 2). Differentiation between cortical and spongy bone can be noted.

DISCUSSION

The ossified auricle is a clinical entity in which the auricle, in part or total, has become stone-hard and moves, if it is not fixed, as a single rigid unit. The most common causes of this condition are local trauma, frostbite, and gout. Systemic diseases such as acromegaly, Addison's disease, collagen diseases, diabetes mellitus, and others are much less common causes of this entity.[1,2] Ectopic ossification is a biologic process in which new bone develops in tissue that normally does not ossify. This new bone has the same x-ray diffraction pattern as the apatite crystals in normal bone and is histologically similar to lamellar bone.[3]

Urist et al[4] reported on the mechanism by which osteoprogenitor cells are stimulated to produce bone by a process that begins with a morphogenetic phase and ends with a cytoreductive phase. Bone morphogenetic protein alters the activity of a previously stable cell population of adult tissue. This extracellular agent may influence mesenchymal type cells with chondrogenetic-osteogenic competence to differentiate into bone-producing tissue.[4,5]

By 1985, fewer than 140 cases of ossified auricle had been described.[5] To date, only 23 cases of calcification or ossification of the auricles in Addison's disease have been reported,[2,5-10] all of them occur-

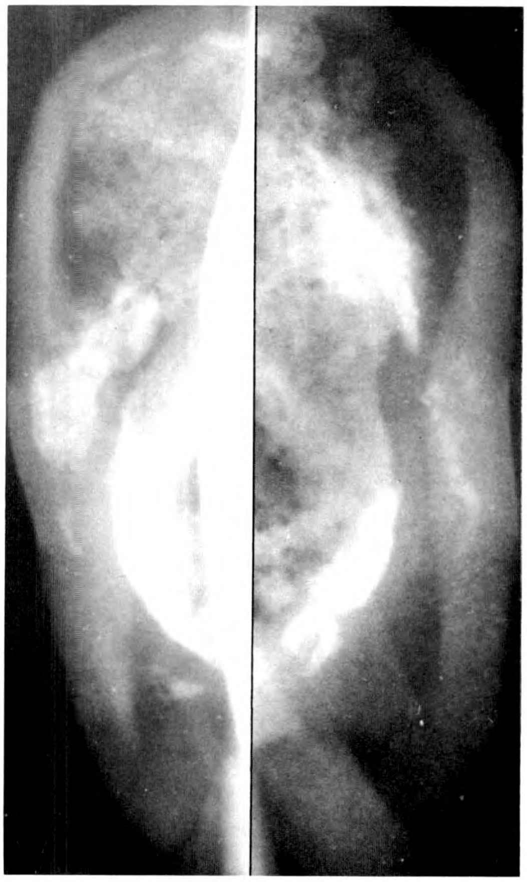

Fig 1. Anterior-posterior film showing both pinnas. Note ossified regions.

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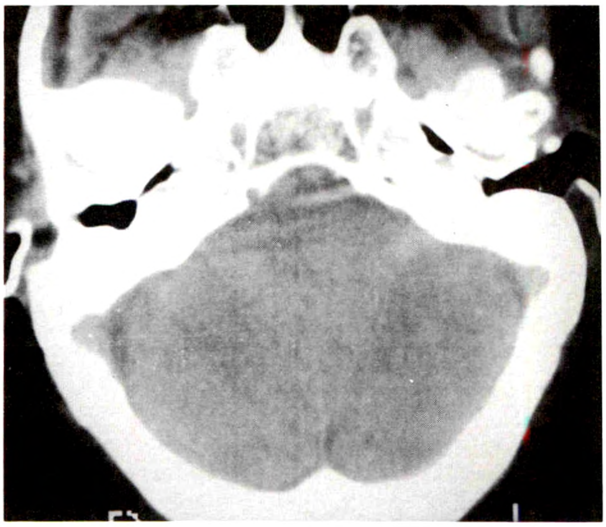

Fig 2. Axial computed tomographic scan.

ring in males. In a radiographic review by Jarvis et al,[7] 6 of 120 Addison's patients demonstrated calcification of the auricle. A true trabecular pattern indicating the occurrence of ossification appeared to be present in some of these patients. True pathologic ossification of elastic cartilages without signs of preceding dystrophic or metastatic calcification has been described in the postmortem examination of a patient with Addison's disease.[9]

The direct cause of ossification in adrenal insufficiency is not yet clear. Metaplastic calcification occurs at other sites in this disorder.[5,7] No hormonal activity has been demonstrated to directly affect this phenomenon, although cortisol deficiency may play a role.[2]

This entity may be more common than could be derived from the paucity of reports discussing the subject. The otolaryngologist is encouraged to palpate the auricles of Addison's patients and could perhaps encounter the ossified auricle, clearly demonstrated by the radiographic examination.

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FUNCTIONAL ENDOSCOPIC SINUS SURGERY
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A course entitled Functional Endoscopic Sinus Surgery — The Messerklinger Technique will be held July 5-7, 1990, in Graz, Austria. For further information, contact Prof H. Stammberger, MD, University ENT-Hospital, Auenbruggerplatz 20, A-8036 Graz, Austria.

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PATHOLOGY CONSULTATION

METASTASES TO MAJOR SALIVARY GLANDS

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Secondary neoplastic involvement of the major salivary glands, most often the parotid, can be from regional (supraclavicular) and distant (infraclavicular) primary neoplasms. Cutaneous squamous cell carcinomas and melanomas are the most frequent offenders, and their numbers dominate all statistics dealing with metastases to the salivary glands and their lymph nodes. Carcinomas of the lungs, breast, and kidneys are the most frequent infraclavicular neoplasms that metastasize to the major salivary glands, and they most often manifest a hematogenous dissemination. Supraclavicular primary disease metastasizes to the salivary glands and their lymph nodes via a more diverse manner: direct extension, lymphatic spread, or, less often, blood vascular transport.

Secondary neoplastic involvement of the parotid and submandibular glands occurs by direct invasion, lymphatic or blood vascular dissemination, or any combination of these methods. Except for the direct incorporation of the glands by contiguous supporting tissue neoplasms and the rarely occurring metastasis of a sarcoma, secondary involvement of these major salivary glands is by carcinomas and melanomas. These are preponderantly cutaneous in origin and primary in sites above the clavicles.[1-4]

The parotid gland is the salivary gland most often involved by secondary deposits. This is, in part, because of the differences in the number and anatomic relationships of the lymph nodes and their drainages of the parotid as opposed to the submandibular glands.[4-6]

DISTANT PRIMARY CARCINOMAS

Metastases from distant (infraclavicular) primary tumors to the major salivary glands or their lymph nodes have usually prompted single case reports because of their rarity. Two studies enlarge our perspective of the frequency of these metastases.[1,7] Table 1, from data compiled by Zachariades[7] in his review of the world literature (principally journals published in English), indicates that 95% of the metastases to the head and neck, exclusive of those to lymph nodes, involve either the bones of the jaws or intraoral sites. Only 18 of 414 metastases from distant primary carcinomas were to the parotid or submandibular glands. The rich resource of 10,944 cases in the University of Hamburg's Salivary Gland Register, supported by a selected review of the literature, provides the data shown in Tables 2[1] and 3.[1] The expected triumvirate of carcinomas of the lungs, breast, and kidneys leads the list. Bloodborne in the main, the metastases most often involve salivary parenchyma rather than lymph nodes.[1,4]

TABLE 1. METASTASES TO MOUTH, JAWS, AND SURROUNDING TISSUES

Site of Metastases	*No. of Cases*
Jaw bones	274
Mandible	203
Maxilla	47
Condyle	24
Intraoral	120
Parotid gland	10
Submandibular gland	8
Submandibular space	2
Total	414

Data from Zachariades.[7]

HEAD AND NECK PRIMARY CARCINOMAS

Patients with potentially metastatic carcinomas of the skin of the head and neck are those with carcinomas of the eyelids and the skin of the frontal, temporal, posterior cheek, and anterior ear areas.[3,8-10] Involvement of the parotid gland by cutaneous carcinomas is influenced by the size, site, histologic type, and invasiveness of the carcinoma, the duration of time prior to treatment, and the adequacy of the treatment. All studies have placed basal cell carcinomas second to squamous cell carcinomas in their involvement of the parotid gland and its lymph nodes. To these we add, in order of

TABLE 2. INFRACLAVICULAR PRIMARY TUMORS WITH METASTASES TO PAROTID GLANDS AND PAROTID LYMPH NODES

Primary Site of Neoplasm	*No.*
Lung	12
Kidney	11
Breast	4
Colorectal	4
Others	
(Stomach; uterus; 1 sarcoma, 1 carcinoma; prostate)	4

Data from Salivary Gland Register, University of Hamburg, Federal Republic of Germany, plus selected literature review.[1]

From the University of Texas M. D. Anderson Cancer Center, Houston, Texas.

REPRINTS — John G. Batsakis, MD, Dept of Pathology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.

TABLE 3. INFRACLAVICULAR PRIMARY TUMORS WITH METASTASES TO SUBMANDIBULAR GLANDS AND THEIR LYMPH NODES

Primary Site of Neoplasm	*No.*
Breast	7
Lung	5
Kidney	4
Others (colorectal, uterus)	2

Data from Salivary Gland Register, University of Hamburg, Federal Republic of Germany, plus selected literature review.[1]

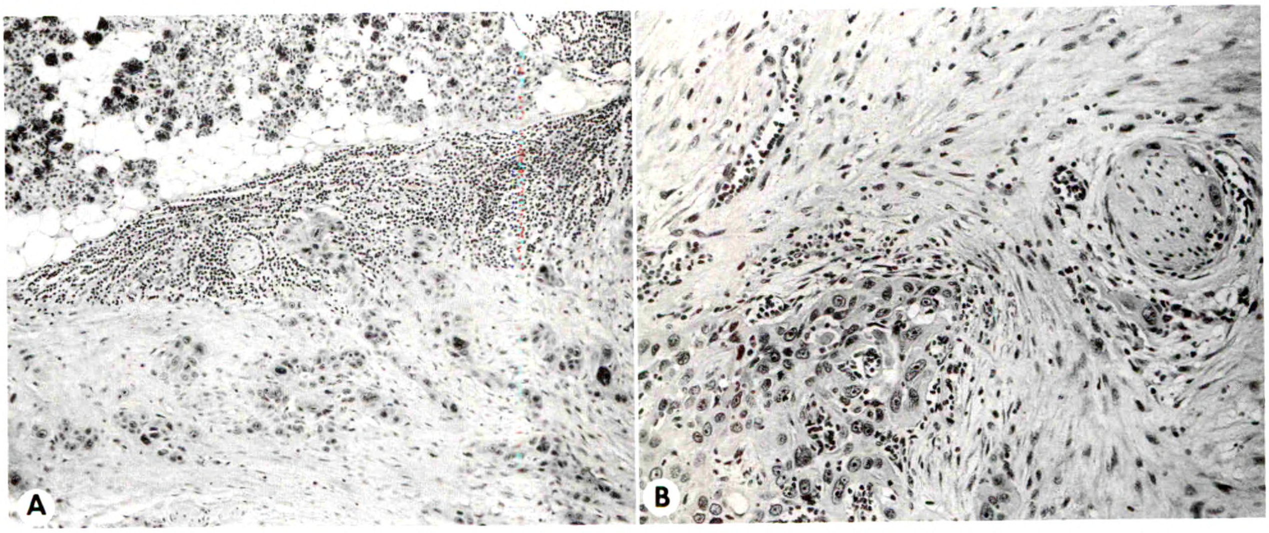
frequency seen at the University of Texas M. D. Anderson Cancer Center, Merkel's cell carcinomas, adnexal skin carcinomas, and sebaceous carcinomas. How often the parotid gland is involved by the two principal offending carcinomas is suggested by the findings of Hanke and Weisberger[11] and Ridenhour and Spratt.[2] The former report that 12 of 1,146 (1.05%) basal cell carcinomas of the head and neck involved the parotid gland; the latter indicate a 1.5% incidence in a series of 2,802 squamous cell carcinomas of the head and neck.

Nearly two thirds of the instances of squamous cell carcinoma involving the parotid gland occur within 1 year after treatment of the primary tumor.[11] Basal cell carcinomas, on the other hand, have a much longer delay between primary treatment and seeding of the parotid gland — an average of 7 to 10 years.[11,12]

There is uncertainty over which mode(s) of invasion is used by basal and squamous cell carcinomas to spread to the parotid gland. This uncertainty is understandable, in that by the time the invasion is clinically manifested, the traces may have been obscured or confounded by the extent of the carcinomas or the tissue changes brought about by prior surgical manipulations. The rarity of lymphogenous or hematogenous metastases from a cutaneous basal cell carcinoma (0.1% in 9,050 carcinomas seen at Memorial Sloan-Kettering Hospital[13]; 0.002% in 50,000 carcinomas reported by investigators at the Royal Brisbane Hospital, Australia[14]) would seem to favor direct extension along vulnerable embryologic fusion planes. Our own experience is similar, in that metastasis to a parotid lymph node is very unusual for basal cell carcinomas. We have found that basal cell carcinomas utilize all other routes, including perineural extension, to invade the parotid gland. Our experience that metatypical basal cell carcinomas, often with considerable desmoplasia, are the principal offenders coincides with the observations of Farmer and Helwig.[12]

There is less uncertainty over the principal route taken by squamous cell carcinomas for involving the parotid gland. Unless the gland is directly invaded by an overlying, deeply invasive squamous cell carcinoma, the first entry to it is usually via an extrafascial or intraparotid lymph node[1,8,9] (see Figure, A). Once metastasis has occurred to a parotid-area lymph node, the carcinoma has access to the lymphatic plexus and to the parotid parenchyma, the facial nerve, and even the parapharyngeal space. In some instances, however, lymph node involvement is synchronous or metachronous with parenchymal spread as the carcinoma expands out of septal and lobular lymphatics or along nerves[4] (see Figure, B).

Squamous cell carcinomas of a number of upper aerodigestive tract sites and the conjunctiva have also been reported to spawn metastases to parotid lymph nodes.[15] Except for metastases from the nasopharynx, so-called bizarre metastases or retrograde spread resulting from either postoperative interruption of normal lymphatic pathways or massive metastases in the neck are held accountable for most of the metastases from mucosal primary tumors.[15] The number of cases of metastases (13) from the nasopharynx in the University of Hamburg Salivary Gland Register[1] should prompt circumspection over



Metastatic squamous cell carcinomas. A) From facial skin in intraparotid lymph node (H & E, original x80). B) In parotid gland (H & E, original x280). Note perineurial invasion and desmoplasia.

TABLE 4. SUPRACLAVICULAR PRIMARY TUMORS WITH METASTASES TO PAROTID GLANDS AND PAROTID LYMPH NODES

Class of Malignancy & Primary Site	*No.*
Squamous cell carcinomas of skin and mucous membranes of head and neck	155
Melanoma (preponderantly cutaneous)	57
Carcinoma from nasopharynx	11
Carcinoma of thyroid gland	2

Data from Salivary Gland Register, University of Hamburg, Federal Republic of Germany, plus selected literature review.[1]

the too-ready acceptance of "primary undifferentiated carcinomas of nasopharyngeal type" in the major salivary glands.

MELANOMAS

Cutaneous melanomas and squamous cell carcinomas of the head and neck account for over 80% of metastases to the parotid glands and their lymph nodes (Table 4[1]). The two neoplasms also share the skin areas most at risk for development of the metastases, and both most often reach the parotid gland/nodes by lymphatic dissemination. Since reports of "primary melanoma" of the major salivary glands border on the anecdotal and are accompanied by nebulous reasoning, it is always safe to consider any melanoma in salivary glands as metastatic, even from a clinically occult primary tumor.[16]

How often melanomas of the at-risk regions invade the parotid gland and its lymph nodes is not known. Relevant reports are weighted because of the referral nature of the reporting institution or the particular focus of the report. In 214 consecutive parotidectomies performed at the University of Bologna over a 13-year period, the incidence of metastatic melanoma to the parotid gland was 1.4% (3/214).[17] Each of these was from a primary tumor that was clinically occult at the time of operation on the parotid. From New South Wales, Australia, it is reported that a 10-year survey of parotidectomies yielded 3 metastatic melanomas in a series of 121 tumors, 39 of which were metastatic squamous cell carcinomas.[18] Caldwell and Spiro,[16] dealing solely with 65 patients who had a parotidectomy as part of the initial treatment for melanomas of the skin of the head and neck, indicate that 1) Breslow thickness correlated poorly with the incidence of parotid metastases, 2) one third of the primary melanomas directly in the drainage area of parotid nodes involved cervical lymph nodes but skipped or bypassed the parotid glands, and 3) 38 of the 65 patients had histopathologically positive parotid lymph nodes in their parotidectomy specimens.

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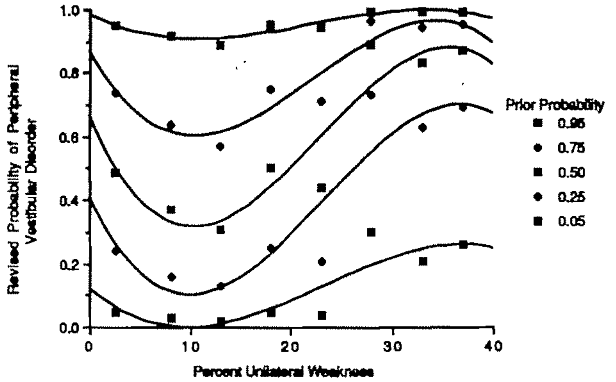
LETTERS TO THE EDITOR

To the Editor:

Using the article by Furman et al on the comparison of alternate and simultaneous binaural bithermal caloric testing,[1] one can measure the value of caloric testing. With data from their receiver-operator characteristic (ROC) curves and Bayes' formula, one can determine the effect of a caloric test result on the clinician's impression that the patient has a unilateral peripheral vestibular disorder.[2]

The Figure below is derived from data from Furman et al's Fig 2B.[1] I assumed that a clinician could assign a probability that the patient had disease before an electronystagmogram was obtained and could put the patient in one of five categories: very likely — .95; likely — .75; somewhat likely — .50; unlikely — .25; or very unlikely — .05.

The authors suggested that the fact that their population with disease was unselected may underestimate the sensitivity of caloric testing. This means that the revised probability of disease for unilateral weakness (UW) greater than 15% to 20% would be underestimated in the Figure. The authors indicated that their no-disease group was "supernormal," and would likely have a greater specificity than a group that might include individuals with asymptomatic vestibular abnormalities. This means that the revised probability of disease for UW less than 15% to 20% would be underestimated in the Figure.



How amount of unilateral weakness affects probability of peripheral vestibular disorder. Outcome of unilateral weakness measurement for binaural bithermal caloric stimulation is shown on x-axis. Five arbitrary prior probabilities of unilateral peripheral vestibular disorder from .05 to .95 are shown. Five curves are polynomial best-fits for revised probability of unilateral paresis based on outcome of unilateral weakness measurement. Look up amount of unilateral weakness on x-axis. From that point on x-axis, go vertically until curve for patient's prior probability of unilateral disorder is reached. From that point on curve, go horizontally to y-axis and read off revised probability of unilateral disorder. For example, 30% unilateral weakness and 50% prior probability of vestibular disorder would yield revised probability of 80%.

On the basis of the above, the reader may consider the following suggestions:

1. Do not order caloric tests on patients very likely (p = .95) to have a unilateral peripheral vestibular disorder, because little information is gained from the test. The maximum change in probability of disease given any test result is about .05.

2. Use the Figure to determine how the test result revises one's estimate of whether or not the patient has a vestibular disorder. Notice that use of an arbitrary cutoff for a positive test, such as 25%, runs the risk of the clinician's concluding that a patient with 24% UW has no vestibular disorder and a patient with 26% UW has a vestibular disorder. This conclusion would be in error, since the revised probabilities of vestibular disorder are similar for these two outcomes.

3. The revised probabilities near 0% UW are probably overestimated. A possible explanation is that Furman et al treated all outcomes as positive numbers, which would skew the results for control subjects, who would be expected to have a Gaussian distribution with a mean of zero UW. With no negative outcomes, the control subjects would no longer have a Gaussian distribution, a requirement for use of ROC curves.[3]

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To the Editor:

I read with interest Dr Mangham's letter in which my article was cited.[1] Dr Mangham's first two suggestions are most helpful. Certainly, for any clinical laboratory test, if there is a high prior probability of a particular disorder, the laboratory test is unlikely to be of much use.

Regarding Dr Mangham's second suggestion, using an arbitrary cutoff runs the risk of false negatives for persons whose test results are near the threshold for normality. Undoubtedly, this risk has engendered the use of the term "borderline normal" for test results near the threshold of normality. This issue underscores the need for physicians to use their clinical judgment when interpreting laboratory data.

Dr Mangham states that a Gaussian distribution is "a requirement for use of ROC curves" and cites an article by Swets.[2] My review of Swets's 1979 paper indicates that ROC curves can be generated regardless of the underlying distribution of the patient and control populations. Dr Swets does indicate, however, that the quantification of the curvature of an ROC curve that is most familiar uses the index d'. This derived measure from the ROC does indeed depend on an underlying Gaussian distribution for the patient and control populations. In my article, however, no such quantification of the ROC curve was attempted and thus no assumptions were made regarding the underlying distribution of the patient and control populations.

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To the Editor:

In reference to the paper by T. N. Kaiser, D. G. Sessions, and J. E. Harvey (Natural History of Treated T1N0 Squamous Carcinoma of the Glottis, *Ann Otol Rhinol Laryngol* 1989;98:217-9), in which a 34.3% incidence of treatment failure was reported in 102 patients treated with irradiation alone at our institution, I would like to offer alternative data and some thoughts on their report. In 1971[1] my colleagues and I reported on 87 patients with carcinoma confined to the vocal cord treated at our institution between 1952 and 1957. There were 6 failures in 53 patients with tumors localized to one vocal cord (12%) and 7 failures in 25 patients with tumor involving the anterior commissure or the contralateral vocal cord (28%). The overall failure rate thus was 13 of 78 (16.6%).

In a subsequent report from our institution by Mittal et al,[2] we updated the figures to include all patients treated until December 1978. Of a total of 177 patients with T1N0 tumors treated, 29 (16%) developed a local recurrence after irradiation, 2 of them also having neck failures. The initial failure rate was 15% in the 119 patients (patients with cord involvement only) and 20% in 58 patients with anterior commissure involvement or involvement of both cords. This incidence is significantly below that reported by Kaiser et al in a smaller number of patients. Perhaps if they had divided their population according to the mucosal extent and depth of the tumor it would have become apparent that the irradiated group included more patients with more extensive lesions.

Second, according to our records 93% of the patients with one-cord or anterior commissure involvement and 77% of those with both cords involved had voice preservation, with an overall voice preservation of 160 of 177 (90%). The mean follow-up in this report was 5.8 years, slightly shorter than the 7 years reported by Kaiser et al. It is difficult to understand that the short additional follow-up should modify the statistics to such a great extent. A better definition of the patient population may shed some light on the differences in therapeutic results. A number of our patients were not referred by the staff of the Department of Otolaryngology, but by physicians outside the Washington University Medical Center with perhaps different criteria for selecting irradiation. A more important point, however, is that in an institutional report comparing more than one modality, representation of all modalities involved in the analysis of the results may contribute to more accurate and objective analysis of the data and reporting of results.

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To the Editor:

In regard to the letter from Dr Perez concerning our article "Natural History of Treated T1N0 Squamous Carcinoma of the Glottis," we have, in a previous letter (*Ann Otol Rhinol Laryngol* 1990;99:419-20), discussed that we are aware that the recurrence rates that we reported for patients treated with radiation therapy were unexpected and perplexing. We noted in that letter that some of the patients who had recurrence were treated by multiple different therapists outside our institution. All the patients in the study had been seen by surgeons in our department and following full evaluation were referred for radiation therapy. Some of those patients exercised their choice to be treated by radiation therapists near their home. Our data indicated that six of the seven patients who so chose developed recurrent tumor, providing evidence for our belief that some therapists produce more effective results than others and mirroring our belief that all things being equal some surgeons produce more effective results than others. It is presently unclear why such a large number of patients with a very curable cancer had locally recurrent disease.

Review of the data indicated that the recurrences were not related to mucosal extent, tumor size (volume), or involvement of specific anatomic structures such as the anterior commissure, the vocal process, or the subglottic area. All of these patients had carcinoma limited to the mobile membranous vocal cord.

We agree with Dr Perez that this brings up certain questions that call for continued in-depth study of subpopulations of T1 glottic cancer, the answers to which may provide science-based treatment recommendations. One possible method to do this would be an authentic prospective randomized study of the treatment of these patients.

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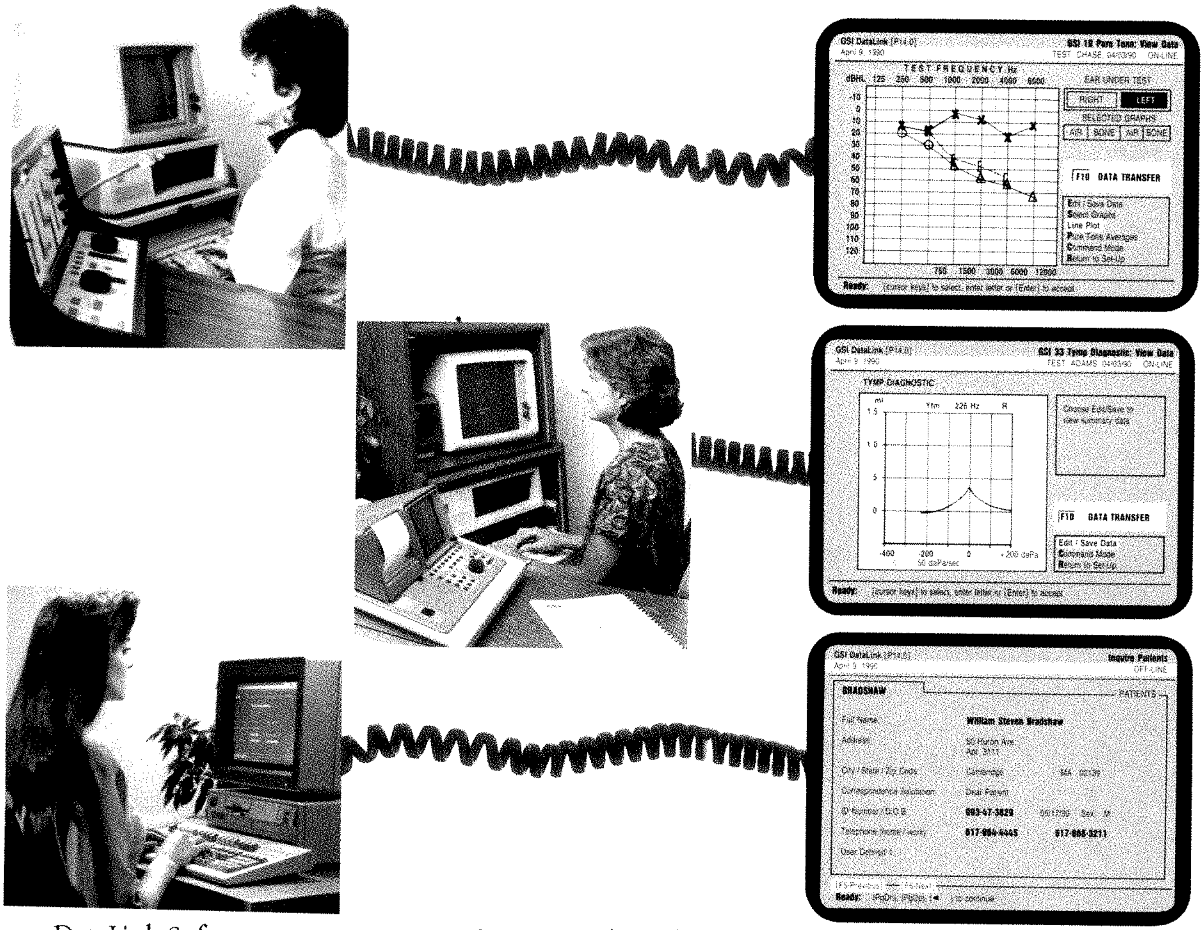

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NONCLOSURE OF PHARYNGEAL MUSCLE AFTER LARYNGECTOMY

NELS R. OLSON, MD ELIZABETH CALLAWAY, MS

ANN ARBOR, MICHIGAN

A prospective study was carried out to evaluate a new technique of pharyngeal repair following laryngectomy. The purpose of this study was to see whether satisfactory healing would occur if the pharyngeal constrictors were not sutured across the closure in the pharynx. If healing proved to be satisfactory the procedure might eliminate the need for primary or secondary myotomy or pharyngeal plexus neurectomy to facilitate tracheoesophageal speech. The results indicate that healing is as good in the group who did not have muscle closure as in those who did.

KEY WORDS — esophageal fistula, laryngeal neoplasms, pharyngeal muscles, pharynx.

INTRODUCTION

After total laryngectomy the usual method of closure of the pharyngeal defect is to close the mucosa and submucosa with two layers of suture material and to close the pharyngeal constrictor muscles over the suture line for reinforcement and strength. This practice is usually taught in most residency programs.

Since the introduction of the tracheoesophageal puncture method of voice restoration it has become apparent that some patients have pharyngeal muscle spasm upon inflation of the esophagus and are unable to talk using this method until a muscle-relaxing or myotomy procedure is carried out.

This study investigates the feasibility of leaving the pharyngeal muscle open as a way of avoiding the need for secondary procedures to facilitate recovery of voice.

PATIENTS AND METHODS

For the last 4 years patients at the Ann Arbor Veterans Administration Medical Center undergoing total laryngectomy for cancer had three different types of operation. One group of patients had a standard laryngectomy with closure of the mucosa and submucosa of the pharynx but leaving the constrictor muscle entirely open ($n = 20$). A second group of patients had a standard mucosal and submucosal closure followed by closure of the constrictor muscles with either unilateral or bilateral pharyngeal neurectomy ($n = 13$). A third group of patients had a standard closure with closure of the mucosa and submucosa, closure of the muscle, and no neurectomy ($n = 12$). Careful review of the postoperative status of all of these patients has been carried out to determine whether the healing characteristics are affected by the nonclosure of the pharyngeal muscle.

RESULTS

Of the 20 patients in whom the pharyngeal constrictor muscles were left open, 2 patients (10%) developed small fistulas that healed spontaneously with dressings only. Both of these fistulas formed in patients not previously irradiated. None of the 4 patients in this group who had preoperative irradiation developed fistulas. Ten patients take a regular diet orally, 9 use a soft diet, and 1 requires tube feeding because of stricture.

In the control group there are 25 patients who had the muscle closed in the usual fashion, 13 of whom had neurectomies. This group suffered 8 (32%) postoperative fistulas. Six occurred in patients who had prior radiotherapy. One of these required a surgical repair. Eleven patients use a regular diet postoperatively, 9 require a soft diet, 2 use a liquid diet, and 3 require tube feeding.

Statistical analysis of the fistula rate reveals that $p > .10$, indicating the difference is not significant. However, the analysis supports the contention that nonclosure does not produce a greater likelihood of fistula formation. Swallowing was initiated at the usual time on the basis of clinical judgment in both groups of patients. No special precautions were taken. Oral feeding usually began 7 to 10 days after operation.

Speech results are not complete as yet, but to date, 9 of the control group are using tracheoesophageal punctures successfully. One required a myotomy before being able to produce voice. In the nonclosure group 5 patients are successfully using tracheoesophageal punctures, and none have had a myotomy.

DISCUSSION

Singer and Blom[1] state that the most serious complication after total laryngectomy is breakdown of

---

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Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, April 28-29, 1990.

the pharyngeal closure with fistula formation. The causes are thought to be infection, suture breakdown, poor quality of tissue due to irradiation or other factors, closure under tension, and lack of wound support. The standard technique of closure following laryngectomy is a three-layer closure with two layers of inverting stitches in the mucosa and submucosa and a layer of sutures in the constrictor muscle complex to reinforce the closure.[2-4] In spite of multiple-layer closure, which includes bringing in constrictor muscles, occasionally the strap muscles, and sometimes the thyroid gland, there is a spontaneous fistula rate of 22% to 50%.[5] Applebaum and Levine[4] found that by using very careful technique, they were able to prevent postoperative fistula in 44 laryngectomy cases. Ten of these patients received radiotherapy prior to operation. They stress a three-layer technique and a vertical line closure if possible. The first layer is a continuous inverting horizontal Connell suture using 4-0 chromic suture material and avoiding entry into the lumen. A second layer of 4-0 chromic sutures is placed and the constrictor muscles are approximated in the midline, also with 4-0 chromic sutures. Antibiotics are used and tube feeding is maintained for 14 days before an oral diet is begun.

In contrast to the stress on careful closure and inclusion of muscle in the closure to prevent fistulas is the evident need for either sectioning the muscle or denervating it in some patients in order to overcome spasm to facilitate tracheoesophageal speech.[1,6-10] Pharyngeal plexus neurectomy has been performed at the time of laryngectomy.[6] A few of our control patients had this done. Baugh et al[9] recommend performance of myotomy at the time of tracheoesophageal puncture placement if high pressures are found with air insufflation of the esophagus. Posterior myotomy of the constrictors at the time of laryngectomy has been recommended.[7] To date, no reports of nonclosure of the constrictor muscles at laryngectomy have been found, although there is a passing reference to it by Hamaker et al.[7] This approach should theoretically eliminate the need for any further intervention in postlaryngectomy patients being fitted with the voice prosthesis. Using this modification, however, depends on proving that it is relatively safe and will not cause increased fistula formation. Other factors such as swallowing ability must also be evaluated.

The present study was designed simply to test one aspect of the problem, that being the rate and severity of fistula formation following laryngectomy if the constrictor muscles are not closed over the suture line in the pharynx. The results indicate that the pharyngeal muscle closure is not essential to prevent fistula formation. The reasons for this are not clear. All 45 patients in this study had similar surgical closures. No special care was taken with the nonclosure group. The one obvious difference is that the skin flap is applied directly to the mucosal closure in the experimental group. Perhaps the skin flap provides as good protection and blood supply as the surgically traumatized constrictor muscles.

CONCLUSIONS

A modification of total laryngectomy in which the pharyngeal constrictor muscles were left open was carried out in 20 patients. Twenty-five other patients operated on during the same period of time were used as controls. The rate of fistula formation in the experimental group was 10%, while it was 32% in the control group. Statistical analysis indicates that the procedure of nonclosure of the pharyngeal muscle is relatively safe. This technical change could result in reduction or perhaps even elimination of postlaryngectomy myotomies or neurectomies to facilitate tracheoesophageal speech.

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LIGNEOUS CONJUNCTIVITIS: AN OPHTHALMIC DISEASE WITH POTENTIALLY FATAL TRACHEOBRONCHIAL OBSTRUCTION

LARYNGEAL AND TRACHEOBRONCHIAL FEATURES

SEYMOUR R. COHEN, MS, MD
LOS ANGELES, CALIFORNIA

Ligneous conjunctivitis is a rare disease of unknown cause characterized by pseudomembranous, fibrous, woody, plaquelike deposits on the conjunctiva. The disease appears to be hereditary and/or familial. Deposits similar to those found in the eye occur in the larynx, tracheobronchial tree, nose and nasopharynx, and vagina. When these lesions occur in the larynx and tracheobronchial tree, voice change and potentially life-threatening obstruction and pulmonary disease may occur. This paper reports the findings in a child with ligneous conjunctivitis who was followed for 1½ years and who had laryngeal and tracheobronchial involvement with voice change and airway obstruction. The literature is reviewed and the histopathologic findings and endoscopic findings and management of the patient are documented. Because the patient had multiple papillomata of both hands, a possible association with human papillomavirus was suspected but never confirmed.

KEY WORDS — alpha chymotrypsin, corticosteroids, drug treatment, heredity, histopathology, ligneous conjunctivitis.

INTRODUCTION AND LITERATURE REVIEW

Ligneous conjunctivitis is a term applied to a rare form of acute or chronic recurrent pseudomembranous or membranous conjunctivitis.[1-3] While the lesion was first reported by Borel in 1833 for the purpose of describing the woodlike consistency of the affliction, Bouisson, in 1847, is credited with its initial identification.[4] This pathologic entity has an acute phase accompanied by nasopharyngitis, vulvovaginitis, and other systemic symptoms.[5]

The disease occurs in the pediatric age group and, with rare exceptions, in children under 3 years of age. At times it occurs in the newborn or very young infant.[1-3] It is more common in the female, with a sex ratio of 3:1. The disease may clear only to recur after a number of years of freedom from symptoms. It remitted for as long as 12 and 15 years in two reported cases.[2] Lower respiratory tract disease (bronchopneumonia) has been reported; however, results of lung biopsies and bronchography have been normal.[6]

The cause of ligneous conjunctivitis is unknown and it has defied every known research attempt to isolate an etiologic agent, whether bacterial, rickettsial, fungal, or viral.[1,2,6-9] Even more discouraging is the poor response to all forms of medical and/or surgical therapeutic measures. Surgical removal of the lesion is frequently met with a rapid recurrence very similar to that which occurs with removal of human papillomata, which tend to recur in areas from which they have been extirpated.[1,3,10,11]

The medical management of the disease has been varied and has consisted of numerous forms of treatment based on presumed etiologic and known histologic factors/or characteristics. Although antibiotics, corticosteroids (topically or systemically), silver nitrate, radiotherapy, and alpha chymotrypsin[2,6,9,10,12-14] have been reported to give temporary relief, none of these forms of treatment can be considered to be curative or to cause remission of the disease.

Histopathologically, the lesion is an accumulation of acid mucopolysaccharides and hyaluronic acid.[8,12] Neovascularization and round cell infiltration with areas positive for alcian blue and periodic acid–Schiff stains are present. The composition of the lesion has led to the use of drugs expected to produce therapeutic benefits; however, none have proven curative.

Lung biopsies done in two patients[6,12] were negative, but the specimens were taken from the lingula. The alveolar sacs were found to be normal. The lesion, however, may be present only in the larger bronchi and/or smaller segmental bronchi. While benign, the lesion may be associated with considerable morbidity.

When the airway is involved, dysphonia and life-threatening involvement of the trachea and bronchi has occurred. Death from pneumonia or severe bronchopneumonia with tracheobronchial obstruction has occurred with episodes of recurrent croup as a result of this disease.[6,9,12] In one family of two siblings, male and female, the girl sibling developed dysphonia and progressive airway obstruction.[13]

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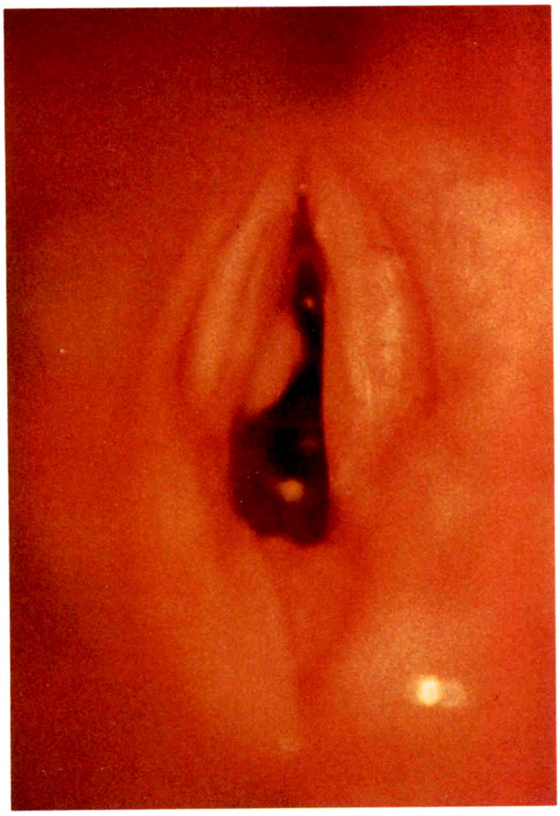

Fig 1. Photograph of larynx taken at direct laryngoscopy. Plaquelike lesion is seen on vocal cord. Subglottic area is also involved.

This patient is herein reported. The disease was considered an autosomal recessive genetic defect.

Another report[14] describes a female infant who suffered from progressive airway obstruction that was associated with ligneous membrane growths of the tracheobronchial tree. This child also had hydrocephalus and required a ventriculoperitoneal shunt. Bronchoscopy in this child showed a circumferential tracheobronchial cast that required 19 endoscopic procedures, in a period of 10 months, for the stripping of these membranes. The child died at 39 months of age of deterioration of pulmonary function.

CASE REPORT

The patient is a female child who was born on April 18, 1979, and when she was first seen in consultation with the pulmonary division of the Childrens Hospital of Los Angeles was 8 years 4 months of age. At 3 weeks of age, this child, who was one of two siblings in a family, a male and a female, was diagnosed as having ligneous conjunctivitis. The child was born by cesarean section. The marriage was nonconsanguineous. Multiple forms of treatment of the conjunctival disease had failed and the disease process improved only slightly after a course of oral ampicillin and a cephalosporin. By 3 years of age, the lesions had progressed to the point of eversion of the lids and required surgical excision. When the child was 5 years of age, dysphonia developed and endoscopic examination of the larynx and tracheobronchial tree was performed at another institution. The findings were variable patches of mucopurulent material in the trachea and bronchi that were adherent to the mucosa. Nodular thickening of the true vocal cords was also noted.

In late March 1987 she developed an upper respiratory tract infection that was associated with severe coughing spasms. The symptoms progressed in spite of treatment with multiple antibiotics for radiographic evidence of bronchopneumonia. Exer-

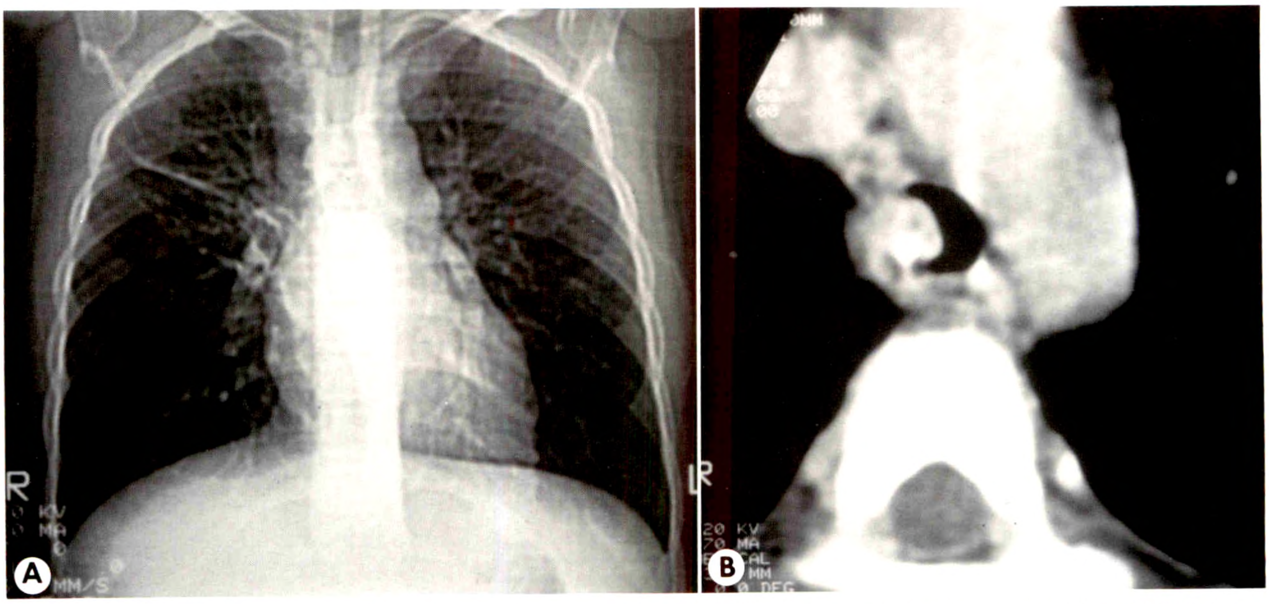

Fig 2. A) Radiograph of chest revealing right upper lobe infiltrate. B) Computed tomograph showing mass in right wall of trachea just proximal (toward the viewer) to carina. There are calcifications within mass, which measures 2 x 1 x 1 cm in size. Mass reduces lumen by more than 50%.

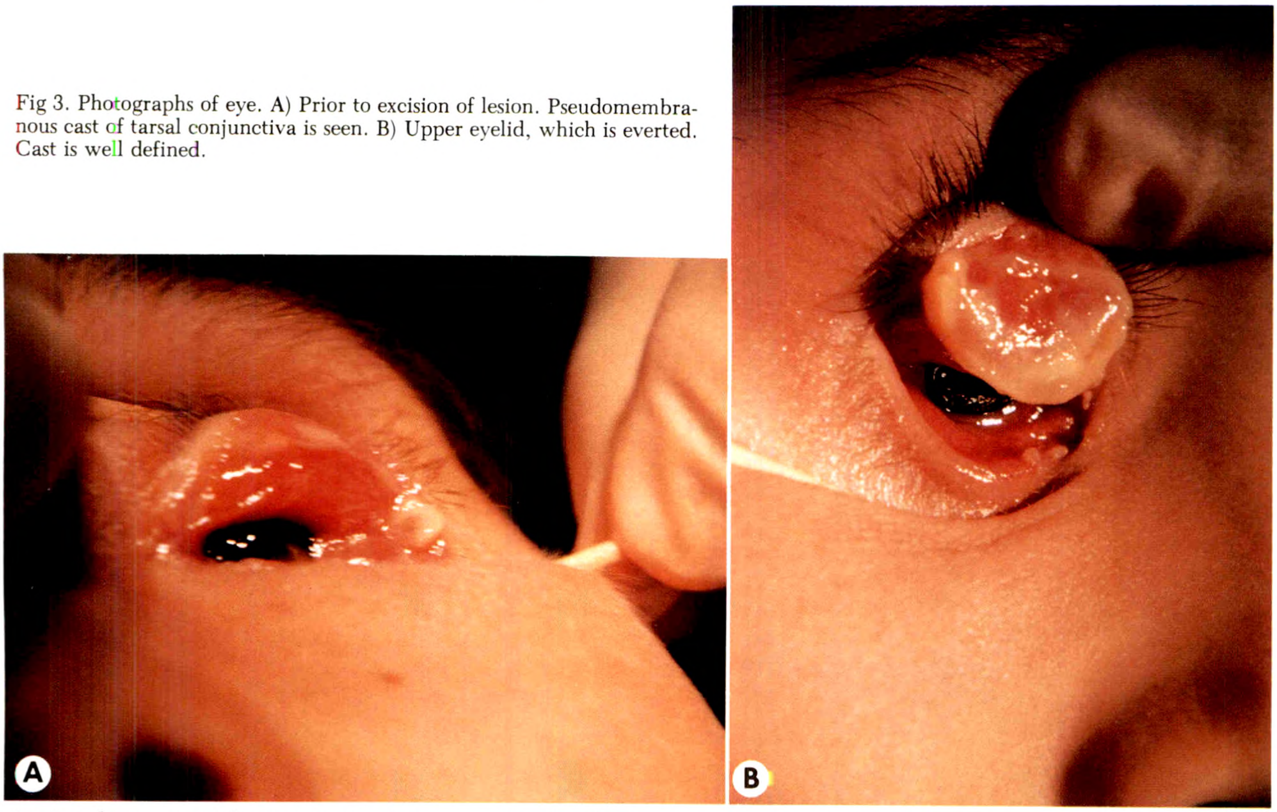

Fig 3. Photographs of eye. A) Prior to excision of lesion. Pseudomembranous cast of tarsal conjunctiva is seen. B) Upper eyelid, which is everted. Cast is well defined.

cise intolerance with severe coughing spasms developed and in June 1987, as a result of these spasms, she developed a pneumomediastinum for which she was treated in an intensive care unit. Steroids and bronchodilators aided in clearing the pneumomediastinum, but there was little apparent improvement in her respiratory condition. She was diagnosed as having asthma and was treated with multiple bronchodilator drugs. In late summer of 1987, while at a children's camp, she developed difficulty in breathing associated with coughing spasms and again was treated with antibiotics that failed to improve her symptoms. Her cough progressed to the point at which dyspnea was so severe her nights were sleepless. Pulmonary function tests revealed restrictive and obstructive findings.

When seen, the patient was a small, slender, but well-developed child who weighed 25.6 kg (35th percentile) and was 127 cm (35th percentile) in length. The positive findings were membranous and pseudomembranous lesions in the conjunctiva, hyperemia of the nasal mucosa, and symmetrical motions of the chest, with a trachea that was in the midline. However, respiratory excursions were small, the chest was resonant, the inspiratory phase of respirations was prolonged, and with rapid breathing, there was a whistling sound audible throughout the chest. A review of the radiographs of her chest showed a right lower lobe pneumonia, a pneumomediastinum with subcutaneous emphysema, and a conelike narrowing above the carina in the trachea. At the time she was considered for endoscopic evaluation, results of pulmonary function studies were reported as normal. However, she had retained residual volume that was markedly increased. Results of a barium esophagram were reported as normal. Further pulmonary function tests showed no restrictive disease and a flow volume loop study suggested extrapulmonary airway obstruction.

On Nov 11, 1987, direct laryngoscopy and bronchoscopy were performed. The larynx was found to be within normal neurologic limits, but the vocal cords were infiltrated with irregular masses of white deposits, especially on the left (Fig 1). The subglottic area and the trachea were also studded with white plaques. A white mass was seen that filled 80% of the tracheal lumen, extending from the lower third of the trachea into the right main stem bronchus. The lesion arose from the posterior, right lateral, and anterior walls of the trachea. The mass was removed with very little bleeding and was surprisingly avascular. The right upper lobe bronchus was then visualized and a small infiltrating lesion was seen within its lumen. This lesion also was removed. There were no postoperative problems and the child was discharged on the day of her endoscopic treatment.

Biopsy of the mass lesion by electron microscopy revealed necrotic debris and histiocytes, the cytoplasm of which was filled with lysosomes. There were no bacteria, fungi, or viral particles identified. The diagnosis was chronic pseudomembranous tracheitis.

The patient was again seen in May 1989 with a recurrence of respiratory obstruction and increased conjunctival pseudomembranous plaques in both eyes. A radiograph of the chest (Fig 2A) revealed a right upper lobe infiltrate and an irregularity of the tracheal air column. A computed tomographic scan with contrast (Fig 2B) showed a nonvascular mass in the trachea above the carina that extended into the right main stem bronchus.

The patient was again submitted to endoscopy and findings similar to those that had been noted at the first endoscopy were present. There was a recurrence of the very large pseudomembranous lesion in the lower end of the trachea that obstructed more than 75% of the tracheal lumen. At the time of endoscopic removal of the occluding mass of the trachea, the conjunctival lesions were removed by the ophthalmologist (Fig 3). Following this operation, the patient has had no airway problems to the date of the writing of this paper.

SUMMARY AND CONCLUSIONS

Ligneous conjunctivitis is a rare disease of unknown cause. The disease is characterized by pseudomembranous, fibrous and woody plaquelike deposits in the conjunctiva. The disease is felt to be hereditary or familial. It is most common in the female child and presents in the newborn and young child under 3 years of age. The disease is refractory to all forms of local and systemic therapy. Surgical removal of the lesion is frequently greeted with rapid recurrences. The lesion may involve the nose, nasopharynx, sinuses, larynx, and tracheobronchial tree. When the deposits become large, serious life-threatening obstruction may occur and voice change is evident. The patient herein reported is a child who required two endoscopic procedures within a period of 18 months in order to remove obstructive pseudomembranous masses. Relief of airway obstruction was obtained with each procedure. Bleeding was inconsequential and the pathologic findings were similar to those seen in the conjunctival lesions. The improvement of the airway was dramatic and on each occasion the child was discharged from the hospital soon after the procedure had been performed.

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USE OF THE NASOGASTRIC TUBE AFTER TOTAL LARYNGECTOMY: IS IT TRULY NECESSARY?

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The nasogastric tube has been routinely used to feed the patient during the first postoperative days after a total laryngectomy. In the last 21 years the author has performed 625 total laryngectomies without using the feeding tube. With this procedure oral feeding could be started during the third postoperative day, making the patient more comfortable and confident. In addition, the hospital stay was shortened. It was also observed that the incidence of pharyngeal fistulas (9%) was comparable to that of other reports in the literature.

KEY WORDS — intubation, laryngectomy, nasogastric tube, pharyngeal fistula.

In spite of all efforts to establish an early diagnosis and to preserve the larynx, total laryngectomy is still the most frequent operation for the treatment of laryngeal cancer. In the surgical technique of total laryngectomy the routine procedure is, after the removal of the larynx, to insert a nasogastric or nasoesophageal tube just before the closure of the pharynx. The purpose of this tube is to secure the patient's proper nutrition during the first 8 to 10 postoperative days, leaving the pharyngeal suture at rest. The nasogastric tube is also believed to decrease the occurrence of the pharyngocutaneous fistula, the most common complication of total laryngectomy. A recent literature review[1] indicates that this fistula is present in 15% to 30% of cases.

In the early days of laryngectomy, just after Billroth showed its feasibility, the nutrition of patients during the first postoperative days was provided through a rectal enema. This practice proved to be inefficient, since it was very difficult for the patients and also because most of the nutrients were expelled soon after introduction.

Probably the first surgeon to use and suggest the use of a nasoesophageal tube was Chevalier Jackson. In a 1904 publication he wrote, "Feeding should be by esophageal tube for a few days until swallowing is easy."[2] In 1914 Gluck and Soerensen[3(p34)] also mentioned the use of a nasogastric tube. Alonso[4] wrote that in "narrow field" laryngectomy, when the suture of the pharynx could be easily done, he did not use a nasogastric tube and started oral feeding on the second or third postoperative day. On the other hand, several surgeons have adopted intravenous feeding on the basis that the nasogastric tube interferes with healing.[1]

Throughout a period of several years we observed that the majority of patients complained of the nasogastric tube as being very unpleasant. For this reason some of them would pull out their tubes during the first 24 hours after the operation. This group of patients was closely watched, and it was noticed that they could swallow saliva without much difficulty. Since 1968, as a result of these observations, we have discontinued the use of the nasogastric tube, feeding the patient by mouth from the third postoperative day on.

Nothing unusual was added to the surgical technique of total laryngectomy in order to abolish the use of a feeding tube. The closure of the pharyngeal mucosa was performed according to the usual method. With 3-0 chromic catgut suture material and an atraumatic needle a continuous inverted suture was made upward, in a straight line. A reinforcement suture was placed over the first one, and the inferior constrictor muscle was closed over it. A hemovac-type drain was placed on each side of the wound. If not enough mucosa was available the suture was done in a T shape.

On the third postoperative day the patients were fed 150 mL of tea every 3 hours. The following day milk and fruit juices were added. If the patients did not complain of pain a soft diet was started on the third feeding day. On the average the patients remained in the hospital for only 7 to 8 days, returning to the outpatient clinic for dressing and suture removal.

Over the last 21 years 625 total laryngectomies were done without the use of any type of feeding tube. All patients were fed by mouth starting on the third or fourth postoperative day. In this group of patients there was a total of 57 fistulas. Of these only 3 fistulas had to be surgically closed. The remaining 54 spontaneously closed between 5 and 38 days after operation. Of these 625 patients, 52 had undergone radiotherapy for curative purposes before operation. This group of patients had a higher per-

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centage of fistulas: 8 of 52 patients (15.3%), versus 49 of 573 (8.5%) in the group without radiotherapy.

In conclusion, our experience indicates that the nasogastric tube is not necessary after a total laryngectomy. Without this tube oral feeding of the patients starts sooner in the postoperative period. For this reason patients become more confident and their hospital stay is shortened.

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LARYNGEAL CHONDROSARCOMA: INCIDENCE, PATHOLOGY, BIOLOGICAL BEHAVIOR, AND TREATMENT

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Chondrosarcoma is the most common mesenchymal tumor of the larynx and approximately 200 cases have been collected in the world medical literature. It is less aggressive in the larynx than elsewhere: cervical or distant metastases are rare (8.5%), and although local recurrences are not uncommon, they are not catastrophic. A retrospective study was made on eight cases of laryngeal chondrosarcoma. Three cases had originally been diagnosed as idiopathic vocal cord paralysis, possibly because of early involvement of the cricoarytenoid joint or the distal portion of the recurrent nerve. This fact emphasizes the need for accurate laryngeal computed tomography in cases of vocal cord paralysis of unknown origin. Surgical excision is the treatment of choice for laryngeal chondrosarcoma, and conservative techniques may sometimes be appropriate. Supraglottic laryngectomy may be the technique of choice in the rare cases of epiglottic involvement.

KEY WORDS — chondrosarcoma, laryngeal neoplasms, sarcoma.

Cartilaginous lesions of the larynx can be classified into neoplastic (chondroma and chondrosarcoma) and metaplastic (chondrometaplasia).[1] The differential diagnosis of these lesions is of paramount importance, because each has its typical clinical course and specific therapeutic and prognostic implications. However, various pathologic and clinical aspects sometimes make accurate diagnosis difficult.

Chondrosarcoma is by far the most common sarcoma of the larynx, although its true incidence is difficult to assess because several cases of low-grade chondrosarcoma have been misinterpreted in the past as chondromas. In 1984, Ferlito et al[2] reviewed 149 cases of laryngeal chondrosarcoma, and about 50 more cases have been recently reported.[2-37]

This study is a retrospective examination of eight cases of laryngeal chondrosarcoma, three of which have already been reported.[2] Review of the pertinent literature is specifically aimed at certain controversial issues, ie, incidence, diagnostic guidelines, biologic behavior, prognostic determinants, and treatment modalities.

CASE REPORTS

Case 1. A 74-year-old man was hospitalized for hoarseness lasting several months and a progressively worsening dyspnea during the previous 3 weeks. Indirect laryngoscopy revealed a tumor in the right hemilarynx, narrowing the laryngeal lumen and covered by an apparently intact mucosa. The right hemilarynx was fixed. Palpation revealed no enlarged cervical lymph nodes in the neck. A biopsy specimen was reported to be chondrosarcoma (grade 2) with a spindle cell component (dedifferentiated chondrosarcoma) (Figs 1 and 2). Histologic examination of the total laryngectomy specimen confirmed the diagnosis of chondrosarcoma.

The clinical course was uneventful and the patient was discharged 15 days after the operation. Postoperative radiotherapy (50 Gy) was administered to the neck. At the follow-up examination 1 year later, chest x-ray studies revealed bilateral lung metastases. Severe dysphagia developed and a large recurrence was found in the hypopharynx.

In the following 3 months, the patient's condition deteriorated, and because normal feeding was impossible, a gastrostomy was performed. Two months later (2.5 years after the operation) the patient died of neoplastic cachexia. An autopsy was not performed.

Case 2. A 50-year-old woman sought emergency hospitalization because of respiratory distress necessitating tracheotomy. During the previous 2 years she had complained of pseudoasthmatic attacks with uncontrollable coughing, tachycardia, and sweating, particularly at night.

Indirect laryngoscopy showed a hard, elastic grayish mass, 2 cm in diameter, invading two thirds of the subglottic lumen. Laryngeal tomograms confirmed the laryngoscopic findings and revealed small, irregular calcifications present within the mass. A biopsy was performed and the mass was histologically classified as a chondrosarcoma. The patient underwent surgical exploration by means of

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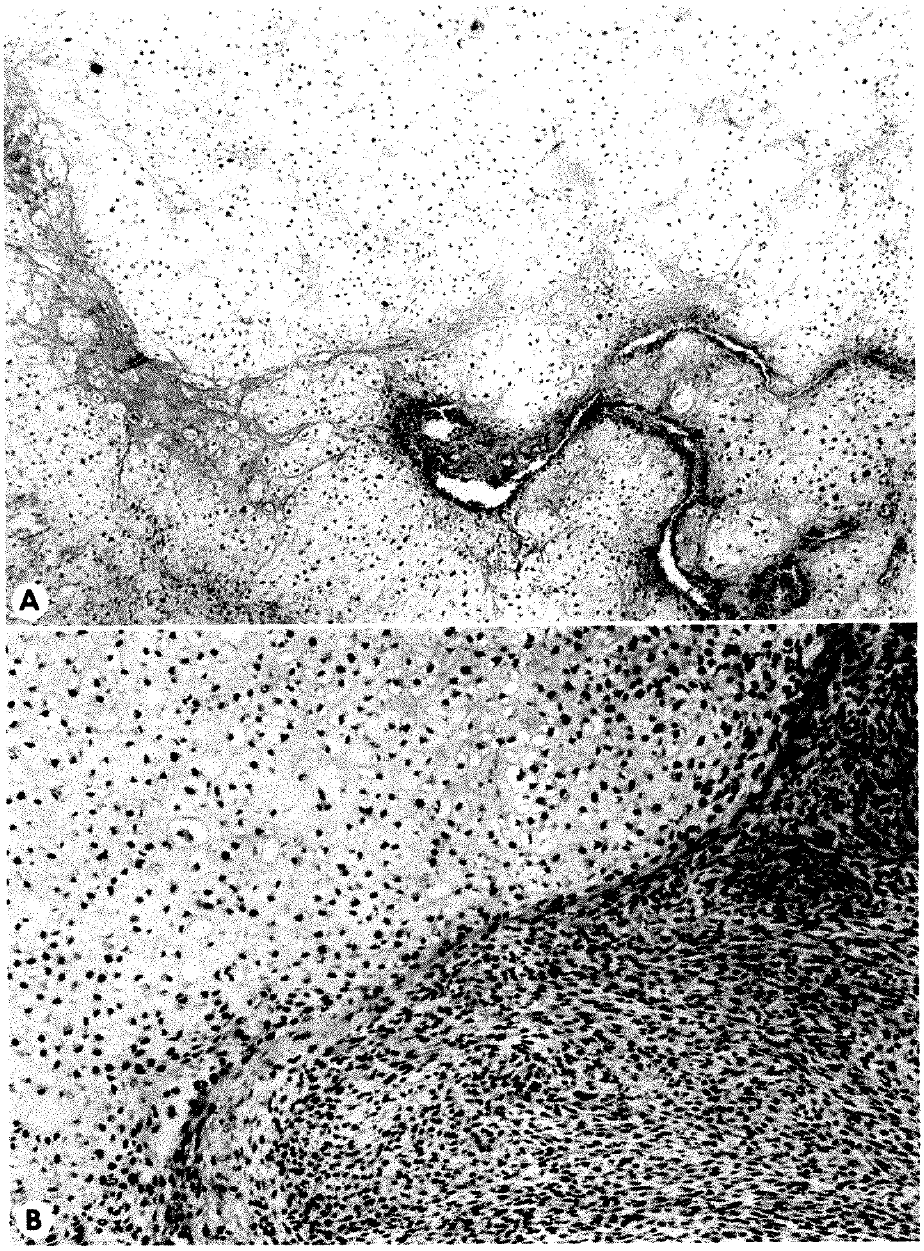


Fig 1. (Case 1) Dedifferentiated chondrosarcoma. A) Panoramic view of cartilaginous component (H & E, original x16). B) Association of cartilaginous and spindle cell proliferation (H & E, original x40).

laryngofissure. The mass, which was mainly implanted in the inner wall of the right thyroid cartilage lamina, was totally resected.

Two years later the patient returned to the hospital for progressively worsening dyspnea. A recurrent tumor was found in the larynx and total laryngectomy was performed. Histologically, the surgical specimen revealed chondrosarcoma (grade 1). Eight years later there was no clinical evidence of recurrent tumor or metastases.

Case 3. A 38-year-old man was hospitalized for fever, severe odynophagia, the sensation of a foreign body in the throat, and mild inspiratory stridor, concomitant with influenza. Indirect laryngoscopy revealed a growth, 2.5 cm in diameter, located on the lingual surface of the epiglottis and covered by a reddened mucosa. Moderate inflammatory edema of the surrounding tissues was also present. Palpation suggested no enlargement of the cervical lymph nodes. Radiographs and laryngeal tomograms showed a mass originating on the lingual surface of the epiglottis with no calcification. Direct laryngoscopy revealed that the growth was particularly hard. Incisional biopsy was performed and the histologic report was chondrosarcoma (grade 2).

The patient underwent supraglottic laryngectomy. Histologic examination of the surgical specimen, in conjunction with electron microscopy, confirmed the diagnosis of chrondrosarcoma (grade 2). Seven years after the operation there was no evidence of recurrence or metastases.

Case 4. A 68-year-old man sought emergency hospitalization for respiratory distress requiring tracheotomy. Two years before, he had started to no-

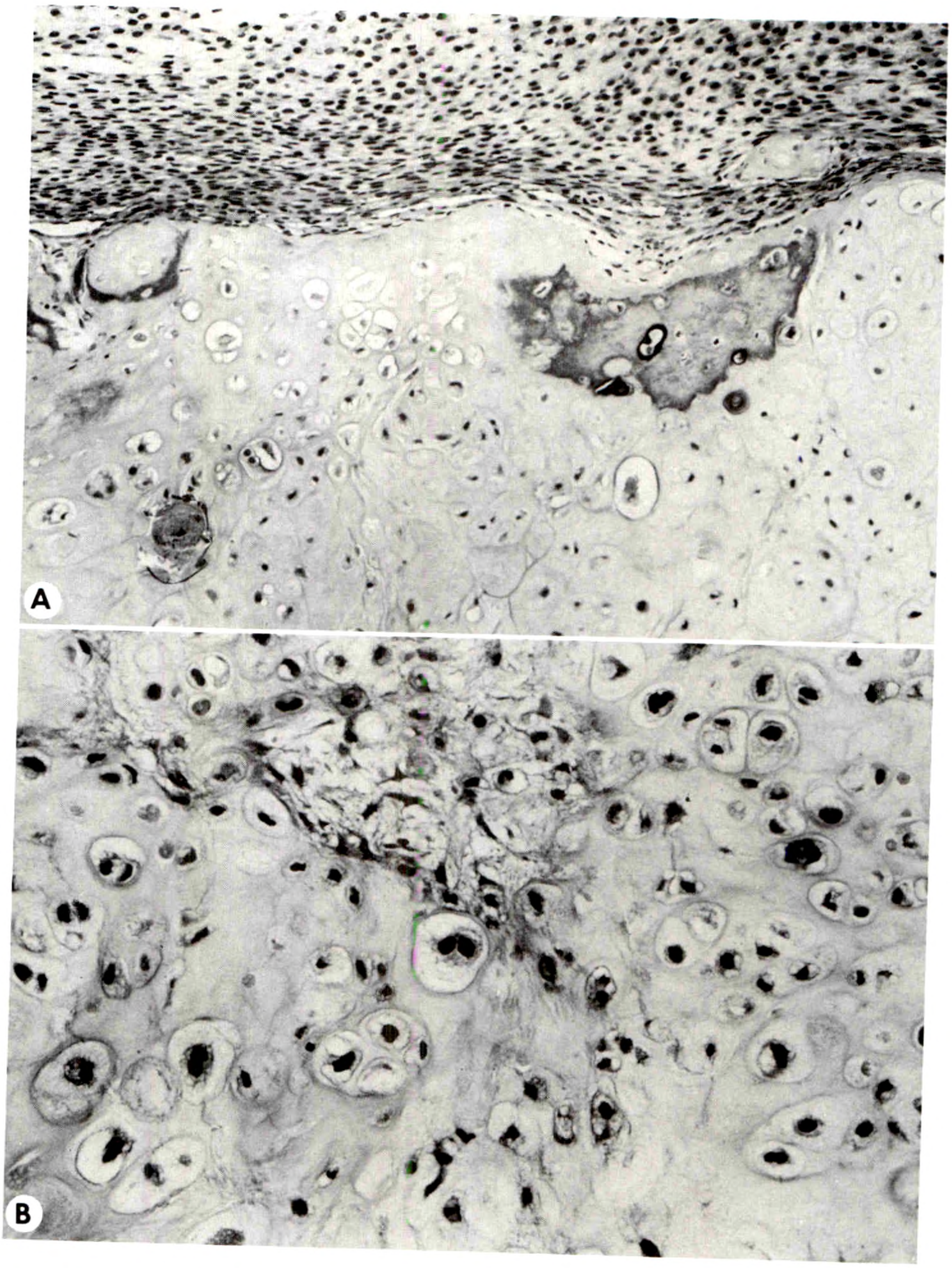


Fig 2. (Case 1) Dedifferentiated chondrosarcoma. A) Calcification within islands of cartilaginous tissue (H & E, original x40). B) Cartilaginous component (H & E, original x100). Note lacunae containing plump irregular cells that are occasionally binucleated.

tice intermittent hoarseness, and a diagnosis of left vocal cord paralysis was made. At that time, results of other diagnostic tests of the head and neck (chest x-rays, barium esophagram, laryngeal tomogram) were all within normal limits.

Indirect laryngoscopy showed a large submucosal mass involving the left hemilarynx and the medial wall of the pyriform sinus. Obstruction of the airway was almost complete and the left hemilarynx was fixed. A biopsy was performed by direct laryngoscopy, but no tumoral tissue was found. A computed tomography (CT) scan of the neck confirmed the presence of a large mass severely narrowing the airway, originating from the cricoid cartilage, which was almost completely destroyed (Fig 3). Calcifications were present inside the mass, but no enlarged lymph nodes were visible.

A CT-guided needle biopsy was performed (Fig 3) and the histologic diagnosis was chondrosarcoma. The tumor was resected, and intraoperative evaluation of its extension inside the cricoid showed conservative surgical excision to be impossible. The final histologic report was chondrosarcoma (grade 2). The patient was alive without disease 2 years after total laryngectomy.

Case 5. A 49-year-old man was admitted for hoarseness of 2 years' duration and 2-day dysphagia. On admission, indirect laryngoscopy showed an extensive submucosal lesion invading the right hemilarynx and narrowing the homolateral pyriform sinus. Two biopsies, both performed by direct laryngoscopy, proved useless for histologic diagnosis.

Study of a frozen section obtained by laryngofis-

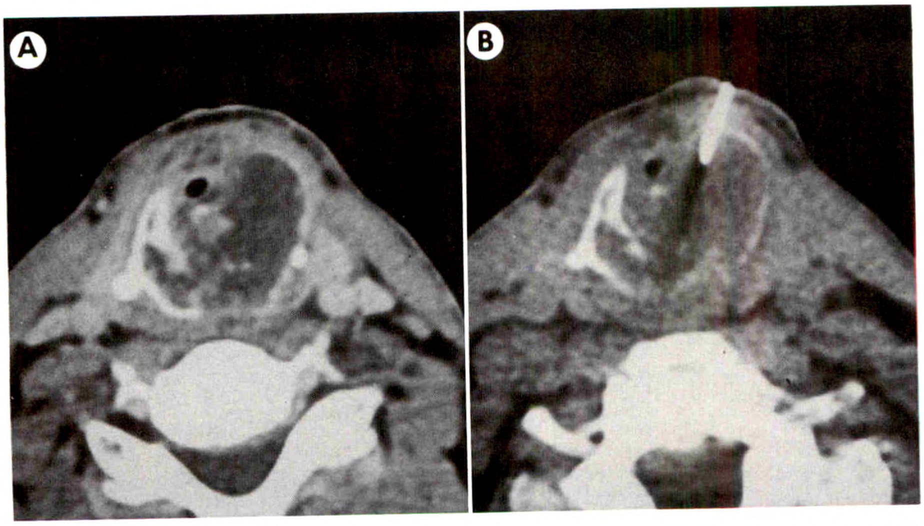


Fig 3. (Case 4) A) Axial computed tomogram showing large, hypodense lesion arising from cricoid cartilage and severely narrowing airway. Calcifications are evident inside mass. B) Needle biopsy was performed under computed tomographic guidance.

sure resulted in a diagnosis of cartilaginous tumor. The right half of the cricoid cartilage was invaded by the tumor and was resected. A stent was left in place for 4 weeks and the patient was decannulated after a further 3 weeks. He remained well for 4 years, until he began again to complain of dyspnea on exertion. Direct laryngoscopy disclosed a submucosal mass mostly involving the residual right hemilarynx and extending to the contralateral vocal cord. A biopsy sample was taken and pathologic evaluation revealed a grade 1 chondrosarcoma. A total laryngectomy was performed and the patient was free of disease when last seen, 2 years after the operation.

Case 6. A 71-year-old woman was referred with increasing dysphagia and shortness of breath of 8 months' duration. A right vocal cord paralysis had been diagnosed 7 years previously. At that time, her workup had included bronchoscopy with washings, chest x-ray study, and CT scan, barium swallow study, neck CT scan, and laryngogram. All tests had proved negative and no biopsy was performed.

Indirect laryngoscopy revealed a large growth involving the right hemilarynx and the adjacent pyriform sinus. The right vocal cord appeared fixed, while the left vocal cord was freely mobile. Tracheotomy was performed in view of the rapidly worsening dyspnea. Direct laryngoscopy confirmed the presence of a hard submucosal lesion for which the final pathologic diagnosis was chondrosarcoma (grade 1).

The patient underwent total laryngectomy. The tumor mainly involved the cricoid cartilage, extending upward to the base of the epiglottis. Pathologic examination of the surgical specimen confirmed the diagnosis of chondrosarcoma (grade 1). The analysis of the surgical specimen, made by means of axial whole-organ sections, demonstrated a large cartilaginous tumor destroying most of the cricoid cartilage but still growing within the external perichondrium (Fig 4). The postoperative course was uneventful and 3 years later the patient remains well, with no evidence of disease.

Case 7. A 62-year-old man presented with hoarseness and stridor. Examination revealed decreased mobility of the right vocal cord and a subglottic mass covered by intact mucosa. A CT scan showed a destructive lesion involving the right cricoid cartilage. Tracheotomy was performed and multiple biopsies were performed with negative results.

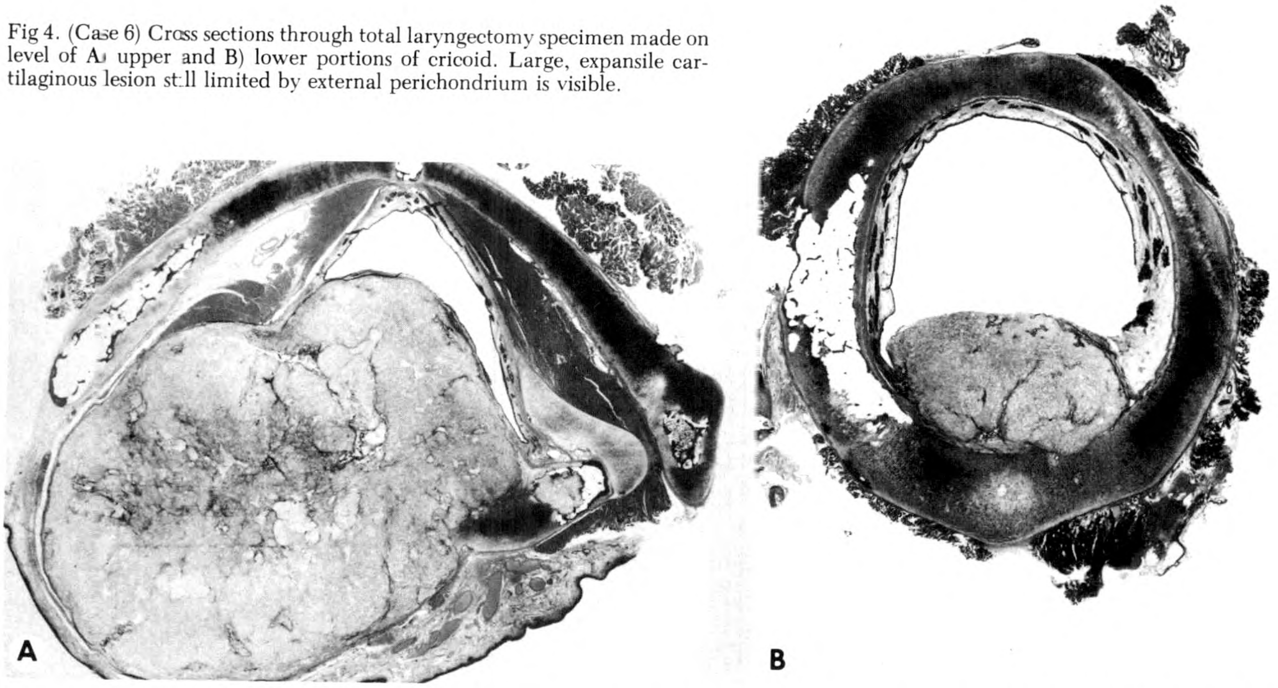
The right side of the neck was then explored and a 2.5-cm cartilaginous tumor was found. The pathologist was unable to make a final diagnosis of malignant tumor from a frozen section; the surgeon therefore debulked the tumor and curetted the portion involving the subglottic space, reconstructing the larynx with a graft from the superior half of the thyroid ala. The final histologic classification was chondrosarcoma (grade 1).

Total laryngectomy was offered to the patient, but he declined; radiotherapy was then considered a suitable alternative. The patient was treated by external beam irradiation by a shrinking field technique (66 Gy), with total remission. Three years later the patient is without clinical evidence of disease.

Case 8. A 37-year-old man was admitted with hoarseness lasting 9 months and a progressively worsening dysphagia over the previous 4 weeks. He had recently noticed the presence of a left cervical mass. The patient was evaluated 4 months before at another hospital, and a diagnosis of idiopathic left vocal cord paralysis was made; a biopsy of the left vocal cord performed at that time was negative for neoplastic infiltration.

On admission, indirect laryngoscopy showed a large submucosal mass involving the retrocricoid area and the left hemilarynx. The left vocal cord was fixed and a slight limitation of the right vocal cord mobility was also evident. A hard, 3.5 x 2-cm mass, apparently originating from the laryngeal

Fig 4. (Case 6) Cross sections through total laryngectomy specimen made on level of A) upper and B) lower portions of cricoid. Large, expansile cartilaginous lesion still limited by external perichondrium is visible.



framework, was palpable in the left cervical area. A CT scan and magnetic resonance imaging confirmed the presence of a massive lesion arising from the cricoid cartilage, posteriorly displacing and narrowing the esophageal lumen. The cricoid cartilage was almost completely destroyed; partial erosion of the inferior part of the thyroid cartilage and of the first tracheal ring was also present (Fig 5A-D). Under CT scan guide a needle biopsy specimen was obtained (Fig 5B); the histologic diagnosis was chondrosarcoma.

Because of the extent of the tumor, a total laryngectomy was performed (Fig 5E,F); intraoperative exploration of the neck was negative for metastatic nodes. Histology of the surgical specimen confirmed the diagnosis of chondrosarcoma (grade 1). Immunocytochemical studies showed a strong positivity for S-100 protein and vimentin, whereas no staining was seen for glial fibrillary acidic protein or epithelial membrane antigen. The immunocytochemical analysis was performed with the avidin-biotin-peroxidase complex immunoperoxidase technique described by Hsu et al.[38] Two months postoperatively the patient is without evidence of recurrence.

DISCUSSION

Chondrosarcoma, and not fibrosarcoma as commonly thought in the past, must be considered the most frequent mesenchymal neoplasm of the larynx,[39,40] and the recent increase in reports of laryngeal chondrosarcoma strongly supports this view. However, the literature is not always very accurate with regard to the actual incidence of chondrosarcoma and of cartilaginous tumors generally. A critical review of cases of chondroma is virtually impossible, because most reports lack pathologic documentation and follow-up data. Accounts of cases in which a primary diagnosis of chondroma was followed by diagnosis of chondrosarcoma for the recurrent tumor lead us to assume that the incidence of chondroma has always been overestimated. For example, only two cases of laryngeal chondroma were seen at the Mayo Clinic between 1910 and 1979 among a total of 33 cartilaginous tumors,[41] and no cases of chondroma were found at the ENT Department of Padua University between 1966 and 1989. This situation, together with the results of a review made by Ferlito et al,[2] is in sharp contrast to the commonly quoted 250 cartilaginous tumors reported in the literature, 28% of which would be malignant.[9,36]

Laryngeal chondrosarcoma most often occurs in patients between the ages of 50 to 70, with a male to female ratio of 3 to 1. The most common site of origin is the cricoid cartilage (75%), especially the posterior lamina. However, there are also reports of its onset in the thyroid cartilage, arytenoid cartilages, epiglottis, and accessory cartilages. Observation of some cases of chondrosarcoma originating from the epiglottis[2,8,24,33,42] disproves the commonly held notion that this neoplasm only occurs in hyaline and not in elastic cartilage.[27]

The most common presenting symptoms of laryngeal chondrosarcoma are progressive hoarseness, dyspnea, and dysphagia, varying according to tumor location. As the neoplasm is usually slow-growing, the patient may adapt to progressive narrowing of the airway until an episode of acute inspiratory dyspnea leads to emergency tracheotomy.[43] When the neoplasm takes origin from the thyroid carti-

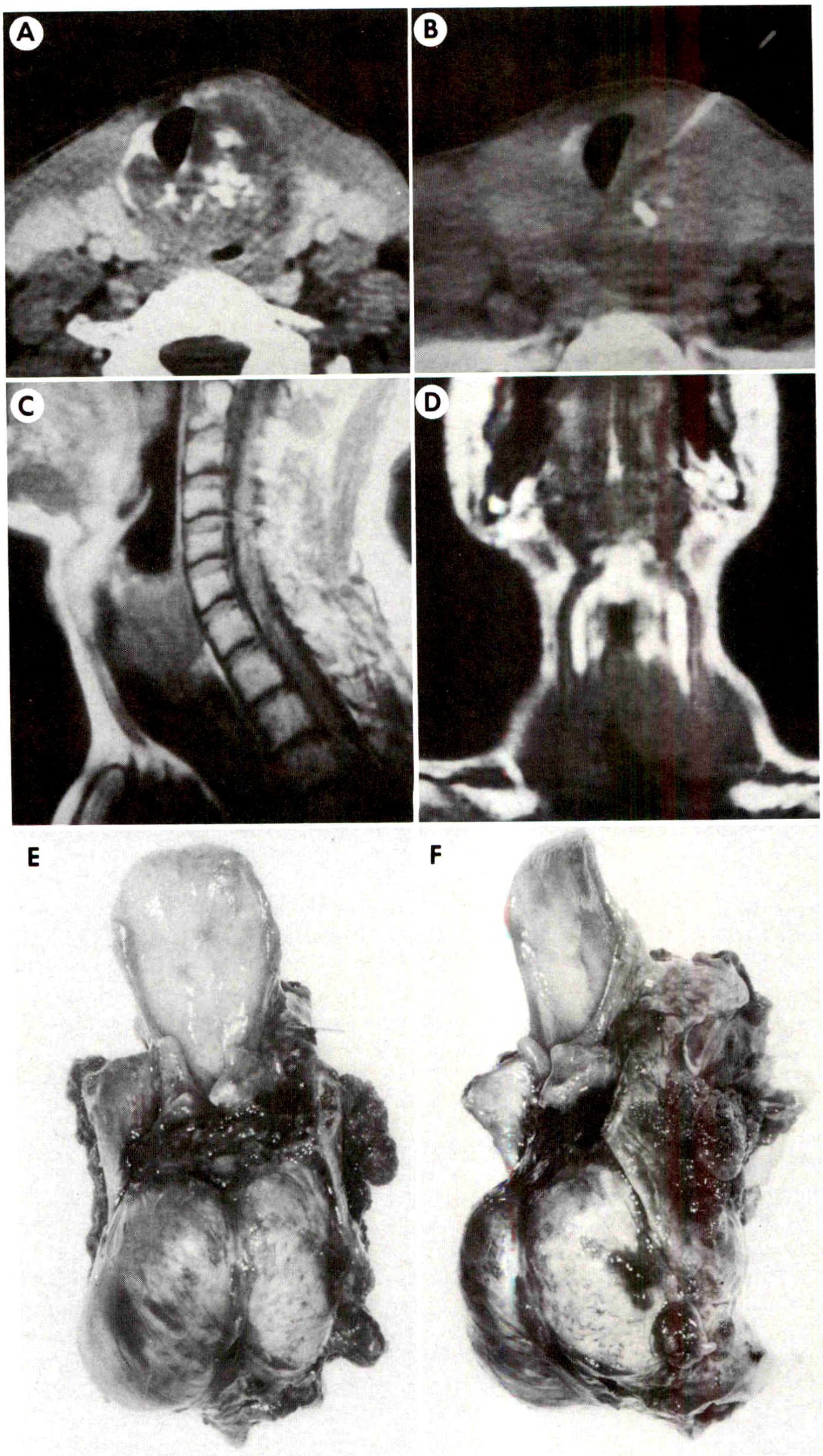


Fig 5. (Case 8) A) Axial computed tomogram demonstrating massive lesion stemming from cricoid cartilage with multiple foci of coarse calcification. B) Needle biopsy was obtained under computed tomographic guidance. C,D) T1-weighted magnetic resonance images. Note posterior extension of tumor, extensive destruction of cricoid cartilage, and partial involvement of both thyroid cartilage and first tracheal ring. C) Sagittal plane. D) Coronal plane. E,F) Views of surgical specimen showing lobulated aspect of tumor originating from cricoid lamina. E) Frontal. F) Lateral.

lage, the major complaint can be the presence of a hard mass in the neck. As found in some cases reported in the literature[19,32] and in three patients in our series (cases 4, 6, and 8), the first clinical sign may be vocal cord paralysis, apparently unassociated with other laryngeal or nonlaryngeal lesions and thus labelled idiopathic. Vocal cord paralysis is almost exclusively an early sign of cricoid chondrosarcoma and may be related to the involvement of the recurrent nerve or to the fixation of the cricoarytenoid joint.

Apart from these cases with no endoscopically visible growths, laryngeal chondrosarcoma usually occurs as a mass covered by intact mucosa. Computed tomography with contrast medium is the best radiographic tool for differentiating cystic (laryngeal cysts, laryngocele) from solid lesions[13] and for leading to the diagnosis of cartilaginous tumor. A lesion with calcified areas, extensively involving one or more cartilages and moderately enhancing after injection of intravenous contrast medium, is a typical CT finding for laryngeal cartilaginous tumor. However, there are no reliable radiographic criteria to enable differentiation between chondrosarcomas and chondromas. Magnetic resonance imaging may be more precise in defining the extension of the tumor and its relationship with surrounding structures, as it also allows a valid resolution in the sagittal and coronal planes.

It is not always easy to obtain an adequate biopsy sample from laryngeal cartilaginous tumors because of their submucosal location and consistency. It is advisable to take the biopsy sample under general anesthesia, and it often proves necessary to perform a preliminary tracheotomy to obtain easier access to the lesion. Laryngeal chondrosarcomas often present areas with different degrees of differentiation, so that only a generous biopsy sample provides reliable definition of the tumor's nature and microscopic features. In two cases in our series (cases 4 and 8), a correct histologic diagnosis was obtained from a needle biopsy under CT scan guidance.

Macroscopic analysis of surgical specimens usually shows a lobulated, submucosal mass of a consistency that varies in relation to the degree of secondary cystic softening.[44] Even in the more advanced stages, the tumor tends to develop within the cartilage and only rarely, or in the case of recurrence, extends beyond the external perichondrium, invading the surrounding tissues.[45-47] Microscopically, chondrosarcoma must be differentiated into low-grade (grade 1), medium-grade (grade 2), and high-grade chondrosarcoma (grade 3).

The histologic pattern of low-grade chondrosarcoma is similar to that of benign chondroma. The neoplasm is composed of abundant basophilic and metachromatic cartilaginous matrices in which the cells show small, densely staining nuclei. Binucleated and occasionally even multinucleated cells may be found. Features of nuclear irregularity and the prominence of nucleoli are also indicative of malignancy. Mitoses are usually absent. Calcification and bone formation are frequent.

Medium-grade chondrosarcoma shows an increased cellularity, particularly at the periphery of lobules. The nucleus-cytoplasm ratio of the chondrocytes is low (cytoplasm is abundant relative to nucleus size). Plump binucleated cells may be frequent and multinucleated cells are also seen. Mitoses, if any, are scarce.

High-grade chondrosarcoma shows pronounced cellularity, and plump binucleated and multinucleated cells are often seen. The chondrocytes have large nuclei with nucleoli and delicate chromatin, and the nucleus-cytoplasm ratio is relatively high. Mitoses are frequently seen.[48]

The results of immunocytochemical studies (case 8) showed a marked positivity for S-100 protein and vimentin.

A particular variant called dedifferentiated chondrosarcoma has also been reported in the larynx.[2,23,28,32] This term indicates a neoplasm in which a spindle cell component is associated with the cartilaginous proliferation. Also in this variant, immunocytochemical investigations for S-100 protein are positive.[23]

Electron microscopy studies have been carried out to substantiate the histologic diagnosis[2,12,33]; nevertheless, in our opinion, their use does not seem to be routinely indicated.

Surgical excision is commonly regarded as the treatment of choice for laryngeal chondrosarcoma. Radiotherapy does not seem to play an important role, although it has been used in the past for recurrent tumors unsuitable for surgical treatment.[42,46] One patient in our series (case 7) obtained clinical remission with a combination of surgical excision and radiotherapy and was disease-free 3 years after diagnosis, but this isolated observation does not allow any meaningful conclusions to be drawn.

Conservative surgical techniques may certainly be considered the mainstay in the treatment of laryngeal chondrosarcoma, but must be strictly applied to ensure that the tumor is radically removed with a wide margin of normal tissue and that the external perichondrium is resected at the level of the lesion. The majority of recurrences observed in the past were probably related to piecemeal excisions sparing the external perichondrium. When the neoplasm takes origin from the epiglottis and involves only the supraglottic region, supraglottic laryngectomy is the treatment of choice. Case 3 in our series is the first to be described in the literature treated by this technique,[2] which has been recently employed also by Jacobs et al.[33] Even in cases stemming from the thyroid cartilage, resection may be obtained through a cervical, extralaryngeal approach.

The problem becomes more complex when one is dealing with cricoid lesions, because this cartilage is considered the keystone in maintaining an adequate laryngeal airway. When the tumor is of limited size and involves less than half of the cricoid, conservative removal through a laryngofissure can be employed. Different techniques have been described to reconstruct the laryngeal lumen and to prevent stenosis.[49,50] Neis et al[36] have recently reported the use of a rib graft after removal of more than half of the cricoid for a grade 1 chondrosarcoma. Although the results of these reconstruction techniques seem encouraging, the number of cases is so limited that no conclusions can be drawn as yet.

A statistically significant evaluation of prognostic determinants and different surgical techniques (conservative versus radical) is hindered by the fact that the data provided in the literature do not allow for comparative analysis between sufficiently homogeneous groups of patients. Lavertu and Tucker[9] compared the results of conservative and radical operations in a total of 46 patients suffering from laryngeal chondrosarcoma and concluded that the difference in terms of cure rate was not significant (77% versus 86%). However, the groups of patients used for comparison varied in regard to the lesion's site, extension, and differentiation and the duration of follow-up.

Generally speaking, the clinical course of laryngeal chondrosarcoma depends on the tumor's degree of differentiation and extension as well as on the adequacy of primary treatment. Grade 1 chondrosarcomas usually show a local malignancy with a minimal propensity for metastasizing. Metastases are more frequent in grade 2 and particularly in grade 3. Lung metastases developed in our case of dedifferentiated chondrosarcoma (case 1), a variant for which prognosis is usually worse in other anatomic regions.[51,52]

Hematogenous and lymphogenous metastases from laryngeal chondrosarcoma are rare and have been observed in 17 cases only,[2,5,8,24,32,33] ie, 8.5%. The lungs were most frequently involved, whereas only eight instances of lymph node involvement were reported. Other metastases occurred in the kidney, spleen, and cervical spine.[2]

Neck dissection is therefore indicated only in cases in which the clinical picture or imaging techniques suggest the presence of lymph node involvement.

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BILATERAL ENDOLYMPHATIC HYDROPS IN MENIERE'S DISEASE: REVIEW OF TEMPORAL BONE AUTOPSIES

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The wide range in incidence rates reported for bilateral Meniere's disease results mainly from the lack of established clinical criteria for bilaterality, and from follow-ups of varying duration. In order to help determine a reasonable bilateral involvement rate, we examined histologic reports of temporal bones with endolymphatic hydrops. We reviewed the literature on temporal bone autopsies from 1938 to 1988, and selected 72 cases for histologic examination. Of the 72 cases, 67 (93%) showed endolymphatic hydrops, 2 (2.8%) showed collapse, and 3 (4.2%) showed membranous labyrinths of normal appearance. Twenty of the 67 endolymphatic hydrops cases (29.9%) displayed bilateral involvement, suggesting a rate of bilaterality in Meniere's disease of approximately 30%.

KEY WORDS — bilaterality, endolymphatic hydrops, Meniere's disease.

INTRODUCTION

Bilateral involvement in Meniere's disease remains a rather poorly researched subject, despite the fact that such involvement can result in severe bilateral hearing loss, recurrent vertigo, and increased disease duration. Even the incidence of bilaterality remains in dispute, with reported figures ranging from 2.3%[1] to 78%.[2] Generally speaking, however, the existing literature indicates occurrence rates in the low to moderate range: 10% (29 of 292 patients),[3] 19% (85 of 452 patients),[4] 25% (75 of 300 patients),[5] 29% (78 of 265 patients),[6] 31.8% (180 of 564 patients),[7] 32% (115 of 360 patients),[8] and 46% (104 of 226 patients).[9] Even among these figures, however, the range is still rather large. The wide variation in reported bilaterality is due to disparities in diagnostic procedure and/or criteria, and to variations in the length of follow-up studies. Without appropriate and objective criteria, a valid assessment of bilateral involvement is impossible.

The first reports of endolymphatic hydrops in Meniere's disease were by Hallpike and Cairns[10] and Yamakawa[11] in 1938; since then, a large body of literature on temporal bone autopsies has been published. In an attempt to determine a reasonable rate of incidence for bilateral Meniere's disease and clarify its clinical features, we examined as much of this literature as possible, directing special attention to cases of endolymphatic hydrops.

MATERIALS AND METHODS

In 1938, the existence of endolymphatic hydrops in Meniere's disease patients was reported by Hallpike and Cairns[10] and Yamakawa.[11] We examined the literature that has accumulated since then on temporal bone autopsies in cases of Meniere's disease, noting especially the patient's sex, age at onset of Meniere's disease, age at the time of death, degree of hearing loss, side of hydrops, and degree of hydrops. After determining the degree of hydrops on the basis of photographs in the literature, we used our slightly modified version of the classification of Paparella et al[12] to group the cases into four levels: normal membrane, mild hydrops, moderate hydrops, and profound hydrops. Since certain authors described the same cases in different reports, we checked each case carefully to avoid duplication.

RESULTS

We examined 72 temporal bone autopsy reports on presumed cases of Meniere's disease. These autopsy cases, selected from 42 sources, are classified chronologically in Table 1[10,11,13-52] according to the report's author; the patient's sex, age at onset of Meniere's disease, and age at time of death; and the side and degree of hydrops. In 4 cases (Nos. 2, 40, 46, and 54) of the 72, only one side was submitted to autopsy; nonautopsied sides are marked in the Table.

Endolymphatic hydrops of some degree was found in 67 of the 72 cases (93%). Of the remaining 5 cases, 2 (2.8%) cases (Nos. 18 and 33) showed collapsed membranous labyrinths, and 3 (4.2%) cases (Nos. 22, 23, and 69) showed normal membranous labyrinths with neither hydrops nor collapse. These five examples having no hydrops were irrelevant to the purposes of this study, leaving us with a sample of 67 hydrops cases.

Twenty of these 67 cases displayed bilateral endolymphatic hydrops. The incidence rate of bilaterality was thus 29.9% (20 of 67 cases).

The sex distribution of the 67 hydrops cases was 42 men (63%) and 25 women (37%). Nine of the 25 women (36%) displayed bilaterality, exceeding the rate for men (26% or 11 of 42) and for the group as a whole (29.9% or 20 of 67).

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TABLE 1. TEMPORAL BONE AUTOPSY REPORTS, 1938-1988 (72 CASES)

Case	*Year of Report*	*Authors*	*Age (yr)*	*Sex*	*Hydrops*		*Age at Onset*	*Remarks*
					Right	*Left*		
1	1938	Hallpike and Cairns[10]	63	M	–	+ + +	60	
2			28	M	X	+ + +	24	
3		Yamakawa[11]	61	M	–	+ +	59	
4	1940	Rollin[13]	48	M	–	+ +	28	
5			35	F	–	+ + +	33	
6			47	F	C	+ + +	41	
7			49	F	+ +	+ +	?	B
8			78	M	–	+ +	?	
9		Hallpike et al[14]	29	M	–	+ + +	28	
10	1942	Lindsay[15]	67	M	+ + +	+ + +	52	B
11	1943	Altmann and Fowler[16]	54	M	+ + +	–	38	
12			52	M	+ + +	+ + +	49	B
13			79	M	+ + +	+ + +	?	B
14	1944	Lindsay[17]	47	M	–	+ + +	44	
15	1946	Lindsay[18]	67	M	+ + +	–	56	
16			55	M	+ + +	–	50	
17	1947	Cawthorne[19]	46	M	+ + +	–	42	
18		Arnvig[20]	76	F	C	C	51	C,R
19	1948	Brunner[21]	68	F	+	+	68	B
20	1949	Day and Lindsay[22]	56	M	+ + +	–	48	
21		Nager[23]	68	M	+ + +	–	54	
22		Berggren[24]	50	M	–	–	?	N
23			40	F	–	–	38	N
24	1950	Wolff[25]	?	M	+ + +	+ + +	?	B
25	1952	Dix and Hallpike[26]	54	M	+ + +	–	43	
26	1954	Hallpike and Harrison[27]	59	F	+ + +	–	57	
27	1958	Lindsay and von Schulthess[28]	66	M	+ + +	+ + +	?	B
28	1959	Lawrence and McCabe[29]	43	F	+ + +	–	39	
29	1960	Seymour[30]	43	F	+ + +	+	37	B
30	1961	Kristensen[31]	66	F	+ + +	+ + +	23	B
31	1962	Schuknecht et al[32]	58	M	–	+ +	48	
32			52	F	+ +	–	49	
33			66	M	C	–	56	C,R
34	1963	Kristensen[33]	83	F	+ + +	+ +	53	B
35	1965	Altmann and Kornfeld[34]	54	M	+ + +	+ + +	?	B
36			59	M	–	+ +	56	
37			70	M	–	+ + +	?	

For hydrops, – indicates none, + indicates slight, + + indicates moderate, and + + + indicates profound.

X — not autopsied, C — collapse, ? — uncertain, B — bilateral hydrops, R — rupture of Reissner's membrane, N — normal membrane.

Continued on next page.

Table 2 presents a comparison by sex of the average onset age of unilateral and bilateral Meniere's disease (63 cases in which age at onset was known). The onset of the disease tended to be earlier in male patients than female.

Table 3 shows the age distribution of Meniere's disease onset for unilateral and bilateral cases (63 cases in which age at onset was known). Both forms displayed peak onset levels during the patients' 50s.

The average duration of the disease, calculated by subtracting the age at the time of onset from the age at the time of death, shows 15.6 years for bilateral cases, longer than the average of 10.6 years displayed by unilateral cases.

The distribution by side of the 47 unilateral hydrops cases shows that the right temporal bone displayed 26 examples (55%) and the left temporal bone 21 examples (45%).

Table 4 presents a breakdown by degree of hydrops of unilateral and bilateral cases. Profound hydrops occurred in 34 of the 47 unilateral cases (72.3%), and in both ears in 12 of the 20 bilateral cases (60%).

The average hearing losses in unilateral and bilateral cases were calculated on the basis of those patients for whom audiograms were available (about half the total number). The average hearing loss recorded for both ears in bilateral cases (62.1 dB) exceeded that of the affected ear in unilateral cases (58 dB).

DISCUSSION

We reviewed 72 temporal bone autopsy reports done on patients with clinically diagnosed cases of Meniere's disease. Of the 72 cases, 67 (93%) displayed endolymphatic hydrops; of the remaining

TABLE 1 (continued). TEMPORAL BONE AUTOPSY REPORTS, 1938-1988 (72 CASES)

Case	*Year of Report*	*Authors*	*Age (yr)*	*Sex*	*Hydrops*		*Age at Onset*	*Remarks*
					Right	*Left*		
38	1967	Lindsay et al[35]	67	M	+ + +	+ +	56	B
39	1968	Schuknecht[36]	65	F	+ + +	+ + +	59	B
40			53	F	+ +	X	51	
41	1969	Black et al[37]	62	M	+ + +	+ + +	26	B
42	1971	Gussen[38]	73	M	+	+ + +	40	B
43			71	M	+ + +	–	52	
44	1972	Kohut and Lindsay[39]	69	M	+ + +	+ + +	44	B
45	1973	Gussen[40]	60	M	+ + +	–	58	
46		Blattler et al[41]	86	M	+ + +	X	45	
47	1974	Gussen[42]	75	M	+	–	41	
48		Schuknecht[43]	59	F	–	+ + +	52	
49			74	M	+ +	–	62	
50			73	F	+ + +	+ + +	72	B
51			86	F	–	+ + +	66	
52			67	M	–	+ + +	62	
53			64	M	–	+ +	63	
54			55	M	+ + +	X	52	
55	1976	Sando et al[44]	55	M	–	+ +	51	
56		Ishii and Kameyama[45]	85	F	–	+ +	71	
57	1977	Schuknecht[46]	58	M	+ +	–	50	
58			71	F	+ + +	+ + +	65	B
59			42	F	–	+	?	
60	1980	Bertrand and Perron[47]	68	F	+ + +	–	45	
61		Belal and House[48]	51	M	+ + +	–	41	
62			71	F	+ + +	–	43	
63			67	F	+ + +	–	57	
64		Belal et al[49]	58	M	+ + +	–	50	
65			71	M	+ + +	+ + +	58	B
66		Fraysse et al[50]	77	F	+ + +	–	57	
67			74	F	+ + +	–	64	
68			85	F	–	+ + +	70	
69			85	M	–	–	60	N
70		Schuknecht and Richter[51]	78	F	+ +	+ + +	73	B
71			87	M	+ + +	–	80	
72	1984	Liston et al[52]	86	M	–	+ + +	53	

For hydrops, – indicates none, + indicates slight, + + indicates moderate, and + + + indicates profound.
X — not autopsied, ? — uncertain, B — bilateral hydrops, N — normal membrane.

5 cases, 2 showed collapse of the membranous labyrinth and 3 showed no abnormalities.

One of the cases of collapse (No. 33 in Table 1)[32] displayed a rupture of the membranous labyrinth, indicating that the collapse resulted from the bursting of an extensively bulging membrane. The diagnosis of Meniere's disease in this case may thus have been correct. The other collapse case (No. 18)[20] had also been clinically diagnosed as Meniere's disease, but its histology more closely resembled that of sudden deafness.

Two of the three cases with normal-appearing membranes (Nos. 22 and 23)[24] seemed to be of central vertigo and not of definite Meniere's disease, because of the increased caloric reactions they displayed while the patients were still alive. The third case (No. 69)[50] had been diagnosed as "probable" Meniere's disease, because the patient's hearing loss was nonfluctuating.

According to these findings, at least four of the five nonhydrops cases above cannot be classified as definite Meniere's disease. The incidence rate of endolymphatic hydrops in the examples of Meniere's disease reviewed in this study thus rises to 98.5% (67 of 68 cases). We can therefore say that clinically definite cases of Meniere's disease almost always display endolymphatic hydrops, with the exception of that small percentage with collapse caused by rupture.

The wide variation in the reported incidence of bilateral Meniere's disease, ranging from 2.3%[1] to 78%,[2] results largely from the lack of established diagnostic criteria. Such criteria vary from author to author, with stricter criteria resulting in lower rates and looser criteria in higher rates.[3] Kitahara et al[6] recommended that all patients be carefully ques-

TABLE 2. AVERAGE YEARS OF AGE AT ONSET, BY SEX

	Endolymphatic Hydrops		
	Bilateral	*Unilateral*	*All*
Male	46.4 (7 cases)	50.1 (31 cases)	49.4 (38 cases)
Female	56.3 (8 cases)	52.0 (17 cases)	53.4 (25 cases)
Total	51.7 (15 cases)	50.8 (48 cases)	51.0 (63 cases)

TABLE 3. AGE BREAKDOWN OF MENIERE'S DISEASE ONSET

Age at Onset (yr)	*Bilateral Hydrops*	*Unilateral Hydrops*	*Total*
20s	2	3	5
30s	1	4	5
40s	3	12	15
50s	5	19	24
60s	2	7	9
70s	2	2	4
80s		1	1
Total cases	15	48	63
Average age (yr)	51.7	50.8	51.0

tioned as to whether they have experienced tinnitus and/or deafness in the contralateral ear during vertiginous attacks; glycerol tests, furosemide tests, and electrocochleographic studies are also helpful. In our study, examinations were conducted histopathologically, not clinically; thus, the problem of appropriate diagnostic criteria for bilateral involvement did not pertain.

Another factor influencing reported incidence rates is the length of follow-up. The longer the follow-up of patients, the higher the incidence rates of bilaterality.[5,6,8] The length of follow-up can be presumed to be sufficient in the cases we considered, as they were all autopsied after the death of the patient. The average age of bilateral cases at the time of autopsy was 66.4 years, as compared to 62.3 years for unilateral cases. The duration of the disease, calculated by subtracting the age at onset from the age at the time of autopsy, averaged 15.6 years in bilateral cases and 10.6 years in unilateral cases. The duration of bilateral cases was thus significantly longer than that of unilateral ones, as previously reported by Kitahara et al.[6]

TABLE 4. DEGREE OF ENDOLYMPHATIC HYDROPS

Degree of Hydrops	*No. of Cases*	*%*
Unilateral		
Profound	34	72.3
Moderate	11	23.4
Slight	2	4.3
Total	47	100
Bilateral		
Profound (both ears)	12	60
Profound and moderate	3	15
Profound and slight	3	15
Moderate (both ears)	1	5
Moderate and slight	0	0
Slight (both ears)	1	5
Total	20	100

Our study found an incidence rate of 29.9% for bilateral endolymphatic hydrops (20 of 67 cases), and we suggest that a figure in this area may be a reasonable approximation for bilaterality. This histologically determined rate corresponds very closely with Stahle and Bergman's[5] rate of 25%, the 29.0% of Kitahara et al,[6] Thomas and Harrison's[7] 31.8%, and Paparella and Griebie's[8] 32%, all obtained clinically.

In our review of autopsy cases, men were found to outnumber women, a pattern opposite to the usual clinical sex distribution of Meniere's disease. This might only reflect a greater willingness on the part of men to donate for autopsy. The percentage of bilaterality in women, though, was much higher than that in men (36% versus 26%).

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MIDDLE EAR AS A GAS POCKET

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An analysis of 45 adult ears that underwent a modified radical mastoidectomy for cholesteatoma and remained with an intact unperforated pars tensa is described. 1) While in practically all these ears some air was present behind the tympanic membrane, its amount varied considerably. 2) The air present behind the tympanic membrane was always in communication with the eustachian tube. 3) The regions in the middle ear devoid of air presented a deep atelectasis that was found predominantly in the posterior-superior part of the middle ear. Topographically the regions of air and atelectasis corresponded to the distribution of ciliated and flat epithelia in the middle ear, respectively. The presence of air in the middle ears obliges us to view these ears as being aerated gas pockets. The aeration difference between such an atelectatic ear and one in a physiologic state is probably a difference of degree. This difference can result from reduction in aeration through the eustachian tube or from excessive absorption of gases into the circulation, or from deficient normal diffusion of carbon dioxide or nitrogen from the circulation into the middle ear, or from a combination of these factors. The analogy with the respiratory system is emphasized.

KEY WORDS — atelectasis, cholesteatoma, middle ear, retraction pockets, ventilation.

INTRODUCTION

A physiologic middle ear (ME) is a gas pocket balanced by diffusion of gases into and from the tissues, as well as by ventilation through and out the eustachian tube (ET).[1-4] For unknown reasons an atelectatic ear contains less gas than a normal ear.[5] Our aim is to study atelectatic ears from the standpoint of a biologic gas pocket.

MATERIALS AND METHODS

MATERIAL

The material comprised 45 adults with cholesteatoma who had undergone a modified radical mastoidectomy within the last 12 years. Their ears presented an intact tympanic membrane (TM) with a variable amount of air space behind it. The amount of air behind the drums was limited by the amount of collapse of the tympanic membrane, and varied from a completely air-filled "tympanum" to a severely collapsed state. None of the drums presented a perforation.

METHOD

Assessment of Amount of Air in Middle Ear. It is difficult to measure precisely the amount of air in the ME in general, and in atelectatic ears in particular. Therefore, the amount of air in the ME was assessed semiquantitatively by arbitrary grading of the degree of collapse of the TM (atelectasis) as follows:

1. Grade 0. Air was present behind the entire TM, as well as in the attic or even beyond it.
2. Grade 1. Air was present behind the entire TM up to the horizontal part of the facial nerve and the facial ridge, yet the attic and mastoid were devoid of air.
3. Grade 2. Air was present behind the TM, except for its posterior-superior quandrant.
4. Grade 3. At least half of the TM, including the regions of the oval and round window, was found to be reclined or adherent to the promontory. The anterior half was filled with air (Fig 1A).
5. Grade 4. Three quarters of the TM was found reclined or adherent to the promontory, yet an anterior-inferior air crescent was present behind the TM (Fig 1B).
6. Grade 5. Anteriorly a cushion or air bubble was seen; the rest of the drum was atelectatic.
7. Grade 6. The TM as a whole was collapsed, with no trace of air found behind it.

Method of Examination. All ears were inspected with the aid of an operating microscope and the Siegel pneumatic otoscope. The examinations were carried out by a senior otologist who used this kind of inspection method routinely.

RESULTS

Aeration of the modified radical mastoidectomies (Fig 2) had the following results. Three of the ears were grade 0; they presented air behind their TMs, as well as in the attic. In addition, one ear presented air posteriorly behind the region of the aditus and the facial ridge going all the way toward the mastoid cavity.

Nine ears were grade 1; they presented a tympanic cavity filled with air, with no atelectasis of the pars tensa. Air filled the entire space behind the TM, starting at the ET and extending to the facial nerve and facial ridge.

Thirty-two ears (71%) presented a retraction or adhesive atelectasis of the pars tensa of grades 2 to 6. The atelectatic, collapsed part was always present in the posterior part of the tympanic cavity.

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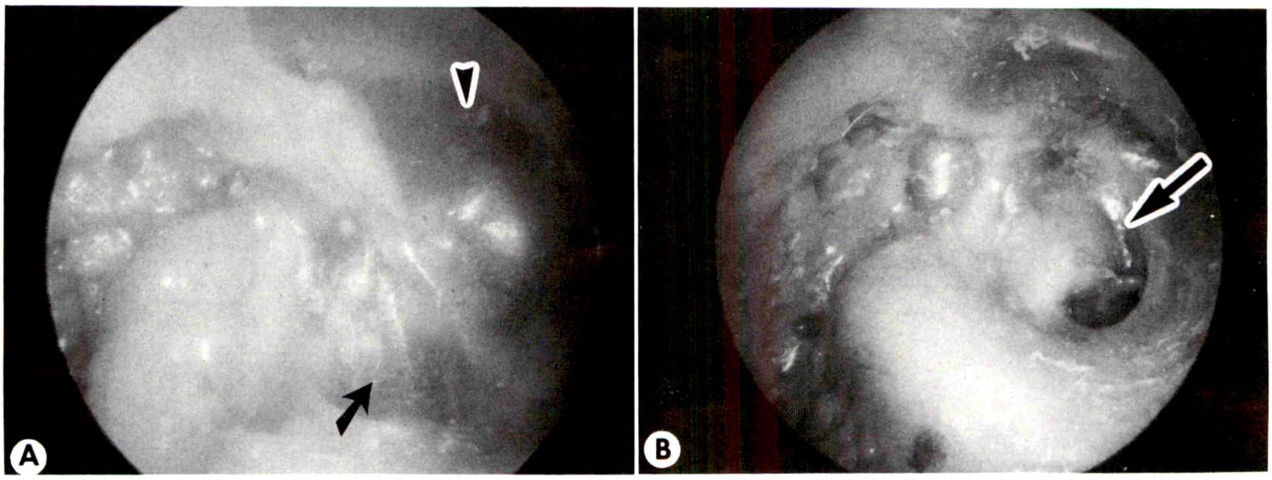

Fig 1. Drums of ears that had undergone modified radical mastoidectomy. A) Posterior half of tympanic membrane (arrow) is reclined on promontory, and anterior half of tympanic cavity (arrowhead) is filled with air. B) Only anterior-inferior air crescent (arrow) exists behind tympanic membrane. This air crescent communicates with eustachian tube opening into middle ear. Rest of tympanic membrane is reclined on medial wall of middle ear.

When all these ears were looked upon as a group, a distinct pattern emerged: the collapsed part of the TM was posterior, while air was found anteriorly. Air behind the TM was found in all ears but one, even if only a bubble was present. This air communicated directly with the tympanic portion of the ET opening (Fig 1). Only one ear was found to be an exception, with no air at all behind the drum — not even at the opening of the ET.

Effusion. Most TMs were opaque to a degree that made viewing through them difficult. Examination with and without the pneumatic otoscope gave the general impression that no effusion to speak of was present behind the TMs of these ears that had undergone modified radical mastoidectomy.

DISCUSSION

The group of ears that we examined constitute pathologically a rather homogeneous group. Preoperatively, these ears harbored cholesteatoma and therefore may be viewed as belonging to a group potentially prone to have aeration difficulties, and may serve as a model for atelectatic conditions.[6] The main feature of atelectatic ears is that they contain less air behind their TMs than normal ears do. The practically invariable presence of some air behind the drums of these ears leads, as we will see, to the inescapable conclusion that these atelectatic ears, like normal ears, are gas pockets, but not closed gas pockets. Closed gas pockets would have eventually contained no air at all or would have been filled with a transudate.[7,8] The question, therefore, is why do atelectatic ears contain less air than ears in the physiologic state do?

GENERAL CONSIDERATIONS

Biologic gas pockets are dynamic structures whose nature and shape depend mainly on the mutual interactions of four basic parameters.[7,9,10]

Diffusibility of Gases. When two compartments containing different gas concentrations are in contact, their gases (in our case nitrogen, oxygen, water, and carbon dioxide) arrive at an equilibrium through diffusion. (While argon is often ignored, its presence in air amounts almost to 1% of the total, and it is usually considered as part of the N_2.) The speed of this diffusion is in direct proportion to the difference in the gases' concentrations (pressures) and in inverse proportion to the square root of their molecular weights.

When equalization of gaseous pressures occurs between a gaseous medium and a liquid medium, the speed of diffusion will again be in direct proportion to the difference in the gases' concentrations (ie, pressures) and in inverse proportion to the square root of their molecular weights. However, in this case an additional factor will play a decisive

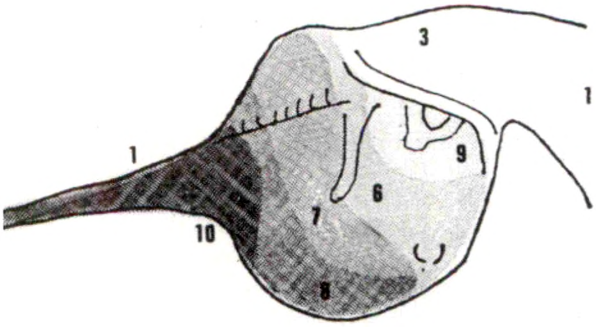

Fig 2. Schematic drawing showing extent of air (shaded area) in 45 middle ears of patients who had undergone modified radical mastoidectomy. Numbers represent number of cases that contain air corresponding to particular gray shading. Note that all ears but one contain air communicating with eustachian tube.

GASEOUS COMPOSITION OF ATMOSPHERIC AIR, MIDDLE EAR, AND VENOUS BLOOD

Gas	*Air*	*Middle Ear**	*Mixed Venous Blood*
Water (mm Hg)	3.7	47	47
Carbon dioxide (mm Hg)	0.3	40-58	46
Oxygen (mm Hg)	159.0	41-94	41
Nitrogen (mm Hg)	597.0	560-632	574
Total gas pressure (mm Hg)	760	760	708

Data from references 7 and 12 through 23.

*Our previous observations of middle ear CO_2 concentration[22] were lower by factor of 2.5, apparently because of leak in measuring method.

role as well, ie, the gases' solubility constant, which is specific for each gas.[10] These circumstances will cause CO_2, which has a high solubility coefficient, to diffuse relatively quickly (within a few minutes) between gaseous and liquid media: 20 times quicker than O_2 and 40 times quicker than N_2.[11] Therefore, "slow" diffusible N_2 is decisive in maintaining a gas pocket in a noncollapsible state when ventilation is not perfect.[9]

Interphase, or Barrier for Diffusion. A thicker partition between the media will hamper diffusion, while the amount of blood vessels, and possibly the speed of blood flow through them, may influence the speed of the gas diffusion.[10]

Pocket's Structure and Framework. Air pockets may possess rigid noncollapsible walls — as in nasal sinuses — or be collapsible all around as the lungs are. In either case the various gas molecules within the pocket will strive to come to equilibrium with the two media bordering its wall, ie, with the venous circulation on the one hand and with the atmospheric medium of the outside world on the other.[7]

The two gas media between which the pocket is sandwiched possess different and therefore "conflicting" total gas pressures as well as different concentrations (partial pressures) of the various different gases that they contain (see Table[7,12-23]). On the outside, air has an atmospheric pressure of about 760 mm Hg, while "inside," the total gas concentration of the venous circulation is considered to be only about 708 mm Hg.[7,12] (The total "gas pressure" in the circulation is not even, forming a gradient from the lungs — where it is similar to the atmospheric pressure — down to about 708 mm Hg when it reaches the venous circulation. In general this gradient is considered to be due to the arterial blood losing more O_2 molecules on its way through the tissue capillaries than it regains CO_2. For a detailed review see references 7, 10, 12, and 24). This difference between the atmosphere and the venous circulation of about 52 mm Hg, as well as the difference in concentrations of each of the various different gases, will create for the gases inside the pocket a constant "pressure conflict" due to the need to reach an equilibrium. The outcome of the above on the pressure and shape of the pocket will be determined by 1) the diffusion process, 2) the nature of the pocket's framework, and 3) whether the pocket will have an opening to the atmosphere, and the nature of this opening.

A completely closed collapsible gas pocket in terrestrial animals will under atmospheric pressure lose all its gases eventually: they will be absorbed into the circulation.[7,12] (Fishes have gas pockets — the swim bladder — with a pressure that may exceed many times their circulation pressure. Most of them have a special organ, the "rete mirabili," that provides for this situation.[25] Several interesting analogies may be found between some of these swim bladders and the middle ear.[25]) Absorption of the gases will occur and continue because they are submitted to atmospheric pressure that exceeds that of the circulation. When some gas is absorbed into the circulation, the pocket's initial atmospheric pressure is reduced. In a collapsible pocket the higher atmospheric pressure will reduce the pocket's size by collapsing its walls. At this moment the pressure in the pocket will increase again to atmospheric level, when more gas will once again be absorbed into the circulation. This process will therefore continue until all the gas in the pocket disappears.[7,12] An example of this situation is seen when a bronchus is completely blocked, leading to a total collapse of the lung.[7]

A noncollapsible closed pocket — as was created experimentally by burying of a rigid semipermeable cage in the tissues[8] — will also have its gases absorbed into the venous circulation. However, as this pocket cannot collapse and its volume cannot be reduced, a negative pressure that cannot be compensated by collapse will form in the pocket. This will call forth at a certain moment a vascular transudate. This process will again continue until no gas is left.

Ventilation. A pocket may be open or closed, and various intermediate situations may exist between a completely open and a completely closed pocket. Also, an open pocket may have a small or large opening, short or long, and may be ventilated passively or actively at various intervals. All these factors will determine the amount of air that passes through the opening, and therefore the gas composition of the pocket.[10]

MIDDLE EAR AS BIOLOGIC GAS POCKET

Although most of the walls of the ME are rigid, it still is potentially a collapsible pocket because of its TM, as seen under atelectatic conditions (Fig 3). When the ET is blocked, intratympanic negative pressure will attract a transudate,[26] once it reaches a negative pressure of 20 to 65 mm H_2O.[26-28] This situation probably hardly exists outside the laboratory. Its main interest is that it is this sort of mechanism that was postulated as the classic ex vacuo mechanism in secretory otitis media.[29]

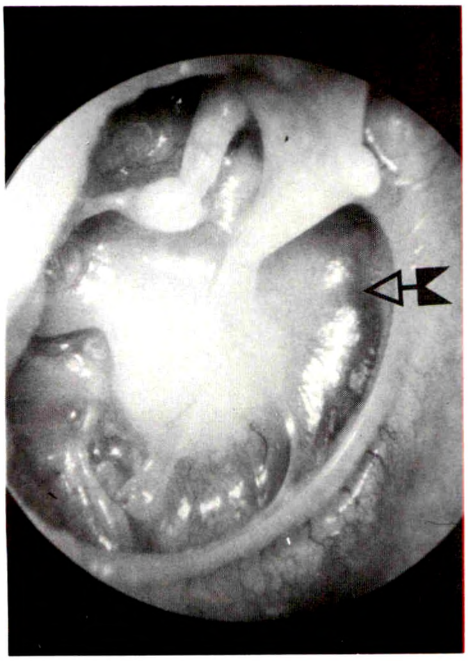

Fig 3. Atelectatic middle ear. Most of tympanic membrane is collapsed. Note air pocket in anterior part that communicates with eustachian tube's opening (arrow).

The pressure in the physiologic ME is atmospheric or close to it, as can be deduced from the noncollapsed position of the drum, as well as from the absence of transudate. This was also confirmed by direct intratympanic pressure measurements.[30,31] We may postulate, therefore, that in the physiologic state the ME output and input of gases are balanced to equilibrate ME pressure with the atmosphere.

Measurement of ME gases is technically difficult and incomplete, yet from what is known today it is obvious that while its pressure is atmospheric,[30,31] the composition of its gaseous mixture differs from the atmosphere, being close to the venous gas contents, ie, CO_2 of 40 to 58 mm Hg and O_2 of 41 to 94 mm Hg (see Table[7,12-23]). (The reported measured values of ME O_2 vary from 5% to 12%, ie, from about 41 to 94 mm Hg, and those of CO_2 vary from 40 to 58 mm Hg. The variations are either due to inaccuracies of measuring small amounts of gases or because their concentrations are not constant [see Table[7,12-23]].) The lower O_2 is nearly balanced by the elevated CO_2 and H_2O vapors (47 mm Hg), and possibly also by elevated N_2.

What kind of gas pocket is the ME? A completely open biologic gas pocket would have an atmospheric pressure, as well as an atmospheric gas composition.[20] This is most probably the case when a large central perforation exists. When the opening narrows down — as in the presence of a ventilating tube — the pressure is still atmospheric, yet a higher CO_2 partial pressure exists (15 mm Hg) because of its rapid diffusion from the circulation.[21] The normal ME, with its atmospheric pressure,[30,31] should also be viewed as an open pocket — though intermittently so, as its ET opens only intermittently, on swallowing, yawning, etc.[32] It is possible that there is only a narrow difference between this pressure-compensated physiologic state and that of the uncompensated atelectatic ear.

ATELECTATIC EAR AS GAS POCKET

Practically all the atelectatic ears reported in this study contained some air in direct communication with the ET. (Similar results in regard to air residue and its distribution were also found by us in a large series of ordinary unoperated atelectatic ears and will be the subject of a separate report.) This finding goes hand in hand with those of previous anatomic studies that showed that the ET, in such conditions, is not closed or blocked.[33] Yet most of these ears (71%) showed a partial collapse of their posterosuperior pars tensa, and all but four were collapsed in the area beyond the facial nerve. A totally blocked ME would have eventually undergone total collapse, with no air residue, or alternatively led to an ear filled with an effusion, as any gas pocket does.[8,26,27] Atelectatic ears may therefore be looked upon as being ventilated through the ET, but insufficiently so, leading to partial collapse of the TM. In fact, clinical experience leads to the impression that even a pinpoint perforation is enough to compensate an atelectatic condition and equilibrate the ME's pressure with the atmosphere.

This insufficient aeration or partially decompensated ventilation may have several origins. First, one may postulate that the amount of gas lost through diffusion into the blood is fixed, while ventilation through the ET may vary. Thus, when ventilation through the ET is pathologically reduced, ME aeration will be insufficient to compensate for the O_2 diffusion, and an atelectasis will ensue.[1,34] The present study, which shows that atelectatic ears usually present air anteriorly in communication with the ET, points toward the capability of the ET to introduce air into these atelectatic ears. This, together with histologic studies showing an open tube in cases of inflammatory ME diseases,[33] speaks for itself and should lead us to look for the origin of air deficiency also elsewhere.

Buckingham et al[2] challenged altogether the classic concept of O_2 absorption from the ME, maintaining that gas is predominantly diffused from the circulation into the ME. Indeed, CO_2 and H_2O are. This is supported by the theory of excessive air loss from the ME through sniffing, which is supposed to cause loss of air through the tube, according to Gray,[35] Magnuson,[36] and Buckingham.[37] That some of the patients do sniff and lose air through the ET is certainly correct,[37-39] yet whether this is the cause of atelectasis has yet to be proven.

As a third alternative to explain ME air deficien-

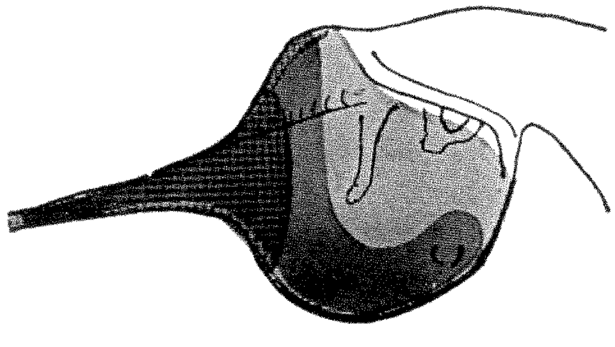

Fig 4. Schematic drawing showing distribution of ciliated epithelium in middle ear. In one third of ears[44] (light gray) cilia, ie, respiratory epithelium, reach region of facial nerve. In two thirds of ears (dark gray) about half of promontory (in crescent form) is covered by cilia. All ears present anterior part of middle ear (ie, very dark) with ciliated epithelium. Note similarity of this ciliary distribution and that of air cushion in modified radical mastoids (Fig 2).

cy, one may consider that ET ventilation is "fixed" but unable to compensate in case of increased O_2 or possible N_2 absorption. Alternatively, it may be postulated that the loss of O_2 through absorption is insufficiently balanced by CO_2 and H_2O (and possibly N_2) diffusion from the circulation into the ME.

The concept that the quantity of ME gases may be influenced significantly through diffusion from or into the venous blood, and that such a mechanism may influence ME's pressure and configuration, is supported by the following: the natural course of atelectatic ears and retraction pockets shows important fluctuations, with at least a third of patients recovering spontaneously.[40-42] Actually, most otologists have observed an atelectatic situation to disappear or even become an overinflated state on a follow-up visit. Lately, we even observed[4] that about 38% of 53 adolescents and adults inflated their atelectatic ears overnight — namely within hours. Such swift waxing and waning of ME aeration cannot be explained but through a very flexible and dynamic process. Frequent and regular ME gas diffusion from and into the circulation has been demonstated to occur,[2,4] and may explain the possible mechanism for such dynamic changes, having its source in nocturnal gas changes in the blood, ie, an increase in CO_2 and a decrease in O_2.[43]

Of exceptional interest in this respect was our study showing[38] that atelectatic ears politzerized with various gases return to their basic atelectatic condition and degree in a time span that corresponded to the gas used. This experiment showed that 1) the gases diffuse from the atelectatic ME into the circulation according to the laws of diffusion, and 2) this diffusion can control the degree of atelectasis, and may therefore play a role in its pathogenesis. The return of an atelectatic ear to its original position has been observed by us also in ears that inflated overnight. All of them returned to their original atelectatic state within about 55 minutes on average.[4]

The predilection of the posterior part of the TM for sinking corresponds topographically to the distribution of the mucosal cells that cover the middle ear mucosa. The anterior part of the ME is dominated by pseudostratified ciliated cells, while the posterior part is covered by flat cells devoid of cilia (Fig 4).[44] We may consider the possibility that the flat cells in the middle ear, situated posteriorly, play a special role in the diffusion of gases. There may be a difference between the anterior and posterior parts of the ME in their ability to be aerated. The anterior part is directly in contact with the opening of the ET and is covered with a relatively thick epithelial lining covered with mucus.[45] The posterior part is covered by thin flat cells through which gas can be easily absorbed, which may predispose to regional collapse of the drum. The lack of cilia posteriorly may also lead to stagnation of inflammatory exudate,[46] with the result of weakening the corresponding part of the TM and predisposing it to collapse.

This study suggests that an atelectatic condition is more complicated than "eustachian tube insufficiency" may imply. Indeed, we should look at the diffusion of gases in and out of the circulation as playing an active role in ME aeration, both in the normal and in the atelectatic conditions. We should also remember that the ME is an extension of the respiratory system, and that in terms of gas diffusion, both systems obey similar physiologic laws.

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IMMUNOGLOBULIN E AND CIRCULATING IMMUNE COMPLEXES IN ENDOLYMPHATIC HYDROPS

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Levels of circulating immune complexes (CICs) in 59 patients with Meniere's disease and total serum immunoglobulin E (IgE) levels in a subgroup of 42 of the 59 were determined quantitatively for possible abnormalities of humoral immunity. Significant differences in average IgE levels between the 42 patients with Meniere's disease and 18 normal control subjects were not determined; however, five (11.9%) of the 42 patients were found to have obviously raised IgE levels. Elevated CIC levels were found in 19 (32.2%) of the 59 patients with Meniere's disease and in one (2.3%) of the 43 control subjects. This difference was statistically significant. The possible mechanisms of immune-mediated endolymphatic hydrops are discussed.

KEY WORDS — allergy, circulating immune complexes, immune-mediated reaction, immunoglobulin E, Meniere's disease.

INTRODUCTION

The causes of endolymphatic hydrops, the typical pathologic change resulting in Meniere's disease, are still obscure in spite of extensive research from various aspects of pathology, biochemistry, anatomy and development, metabolism and endocrinology, and genetics. Allergic or immunologic mechanisms often are postulated for diseases of unknown cause. According to Clemis[1] and Powers,[2] as early as 1893, Quinke first advocated the theory of allergy as a cause of endolymphatic hydrops. However, a direct cause-and-effect relationship between Meniere's disease and allergy was first demonstrated by Duke[3] in 1923. His observations were verified by many authors throughout North America.[4-6] Since McCabe's[7] clinical report on autoimmune sensorineural hearing loss in 1979, it has been suggested that autoimmunity may be important as the cause of some cases of Meniere's disease.[8,9] Recently, Brookes[10] reported that more than half of his patients with Meniere's disease had elevated levels of circulating immune complexes (CICs) and suggested that type III allergy reactions mediated by autoimmune complexes probably played a causative role in the pathogenesis of endolymphatic hydrops.

The present study was undertaken to reexamine the roles that type I allergy mediated by IgE and type III allergy mediated by immune complexes might play in the pathogenesis of endolymphatic hydrops.

MATERIALS AND METHODS

Subjects. The patients with Meniere's disease were diagnosed according to the American Academy of Otolaryngology–Head and Neck Surgery 1985 criteria.[11] There were 59 patients in all, 29 men and 30 women, with a mean age of 42.2 ± 11.0 years (range, 23 to 69 years). The average duration of the disease was 6.5 ± 6.2 years (range, 0.5 to 24 years). The disease was bilateral in 17 (28.8%) cases. Sera obtained from all 59 patients were assayed for CICs. Forty-two of the 59 patients, 23 men and 19 women, with a mean age of 41.3 ± 10.8 years, were selected randomly as subjects for total serum IgE measurement.

During the same period, 43 normal control subjects also were studied (mean age, 38.5 years; range, 29 to 58 years). Circulating immune complexes of all the 43 control subjects were assayed, whereas IgE was measured in 18 randomly selected control subjects (12 men and six women; mean age, 43.3 years).

Measurement of IgE Levels. An enzyme-linked immunosorbent assay (ELISA) was employed for the measurement of IgE levels. In brief, disposable polystyrene 40-well microtiter plates were coated with sheep anti human IgE diluted in carbonate-bicarbonate buffer, pH 9.6. The plates were incubated in a moist chamber overnight at 4°C. Phosphate-buffered saline, pH 7.4, containing 0.05% Tween 20 was used in washing, which was followed immediately by adding appropriate dilutions of sera from the subjects. Positive control wells were filled with IgE standards of known concentration at the same time. After incubation in a moist chamber at 37°C for 2 hours, the plates were washed three times and horseradish peroxidase–conjugated sheep anti human IgE was added at a predetermined dilution. After incubation at 37°C for 2 hours and three washings, 200 µL of ortho-phenylenediamine (OPD) substrate (4 mg OPD in 10 mL phosphate/citrate buffer, pH 5.0, with 15 µL of 30% hydrogen dioxide) was added to each well. Thirty minutes later, the colorimetric reaction was stopped by adding 50 µL of 2 mol/L sulfuric acid to each well, and then the reaction was read at 490 nm

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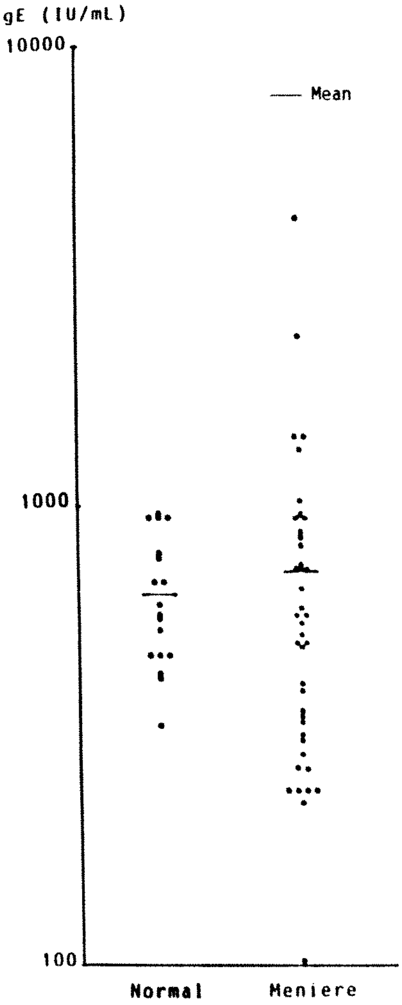

Fig 1. Total serum IgE levels in patients with Meniere's disease and in normal control subjects.

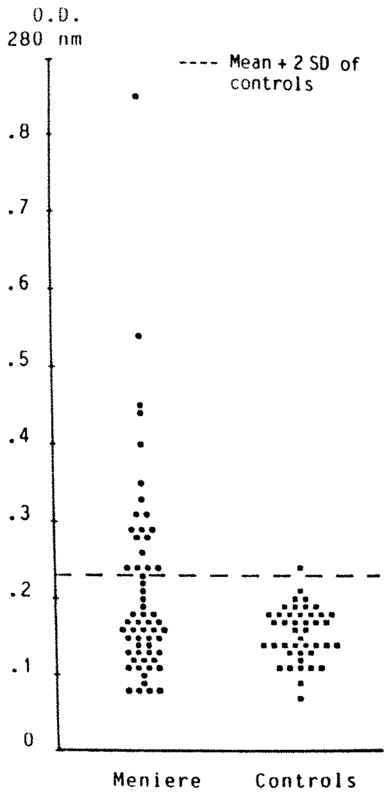

Fig 2. Levels of circulating immune complexes in patients with Meniere's disease and in normal control subjects. O.D. — optical density.

with a micro-ELISA minireader (model MR590, Dynatech, Alexandria, Va). Each measurement was performed in duplicate. The ELISA kits were provided by the Department of Immunology, Institute of Basic Sciences, Chinese Academy of Medical Sciences.

Measurement of Levels of Circulating Immune Complexes. The polyethylene glycol (PEG) precipitation test described by Digeon et al[12] was used in the quantitative measurement of CIC levels. Polyethylene glycol precipitates were dissolved in borate buffer (0.1 mol/L), and the immunoglobulin components (IgG, IgM, and IgA) in the immune complexes then were analyzed by single radial immunodiffusion.[13]

RESULTS

Total Serum IgE Level. The mean level of the 42 patients with Meniere's disease was 731.9±680.0 IU/mL (IU = 2.42 ng), compared with 653.0± 202.2 IU/mL of the 18 normal control subjects. A statistical analysis (*t* test) did not find any significant differences between these two groups ($p > .05$). However, five (11.9%) of the 42 patients with Meniere's disease had obviously elevated IgE levels that were more than 3 SD above the mean level of the normal control subjects (Fig 1).

Levels of Circulating Immune Complexes. Overall, 19 (32.2%) of the 42 patients with Meniere's disease had significantly elevated CIC levels that were more than 2 SD above the mean levels of the control subjects, whereas this was true for only one (2.3%) of the 43 control subjects (Fig 2). This difference was statistically significant ($X^2 = 14.1$, $p < .005$). Of the 19 patients with raised CIC levels, 11 had bilateral hearing loss, and they accounted for 64.7% of all 17 patients with bilateral hearing loss; eight had unilateral hearing loss and accounted for 19.1% of all 42 patients with unilateral hearing loss. The difference between bilateral and unilateral groups was significant ($X^2 = 11.6$, $p < .005$). Table 1 suggests that the degree of hearing loss seemed to be highest in the patients with raised CIC levels.

Table 2 shows the number of Meniere's patients and control subjects in whom the immunoglobulin components in CICs could be quantitatively detected and the mean levels of the immunoglobulin components (IgG, IgM) in CICs. The mean complexed IgG and IgM levels in the Meniere's group were significantly elevated (*t* test, $p < .01$). Combined IgA levels could not be detected in either patients or controls and thus are not shown in Table 2.

TABLE 1. CORRELATION BETWEEN FOUR-FREQUENCY PURE TONE THRESHOLD AVERAGES AND PATIENTS WITH RAISED LEVELS OF CIRCULATING IMMUNE COMPLEXES

PTA (dB)	*No. of Patients*	*No. of Patients With Raised CICs*
0-20	6	1
21-45	25	5
46-70	22	9
71-90	5	3
>90	1	1

PTA — pure tone threshold average of hearing on worse side, CIC — circulating immune complexes.

DISCUSSION

Many clinicians agree with Duke[3] that allergy is one of the important causes of Meniere's disease. Pulec[14] felt that the cause of Meniere's disease in 14% of his patients was an allergy. Stahle,[15] who did not find higher levels of IgE in the serum of Meniere's group as compared with the levels in the normal group, however, ruled out the possibility of immediate-type allergy in Meniere's disease. In the present study, our failure to find significant differences in the mean levels of serum IgE between the Meniere's patients and normal control subjects (Fig 1) corresponded with Stahle's[15] results. On the other hand, we found that five (11.9%) of the 42 patients with Meniere's disease had obviously elevated IgE levels (Fig 1). Therefore, it was suggested that immediate-type allergy might play an important role in the cause of Meniere's disease in these particular patients.

Recently, Miyamura et al[16] reported that IgE-mediated allergic reactions induced a transient endolymphatic hydrops in guinea pigs by introduction of antigens into the inner ear through the facial nerve canal after passive sensitization of the animals with antisera against the same antigens. Miyamura et al also confirmed the presence of degranulating mast cells around the capillaries in the subepithelial connective tissue of the endolymphatic sac. However, it is generally unknown whether the degranulation of the mast cells in the sac is mediated by elevated serum IgE levels. Since the serum IgE levels in atopic patients fluctuate significantly according to the different stages of the disease, further research is necessary to clarify the significance of total serum IgE levels in the relationship between immediate-type allergy and endolymphatic hydrops.

While otologists were in a dilemma to explain the role that immediate-type allergy might play in endolymphatic hydrops, a type III allergy hypothesis was advocated by Hozawa[17] in Japan in 1980. Hozawa observed the labyrinthine reactions induced by introduction of chicken serum through the left stylomastoid foramen in rabbits sensitized by the same antigen. The positional nystagmus observed bore a striking resemblance to that of a Meniere's attack. Electrocochleography showed a pattern of cochlear impairment, and histologic study revealed endolymphatic hydrops in the challenged ears. A type III allergy mechanism was suspected as being responsible for these findings.

TABLE 2. IMMUNOGLOBULIN COMPONENTS IN CIRCULATING IMMUNE COMPLEXES

	IgG (mg/dL)		*IgM (mg/dL)*	
	*n**	$\bar{x} \pm SD$	*n**	$\bar{x} \pm SD$
Patients with Meniere's disease (n = 59)	46	36.6 ± 33.3	52	22.9 ± 9.1
Control subjects (n = 43)	35	18.5 ± 1.6	39	15.1 ± 3.5
t test		p < .01		p < .01

*Number of subjects in whom immunoglobulins in circulating immune complexes could be quantitatively detected.

Further evidence for endolymphatic hydrops induced by type III allergy damage to the inner ear was presented by Harada et al,[18] who immunized guinea pigs with tissues from around the stria vascularis of normal rabbits in complete Freund's adjuvant. Development of endolymphatic hydrops was observed in four of 11 animals, but hydrops failed to form in C4-deficient guinea pigs that were immunized in the same manner. Harada et al also found IgG and complement in the inner ear fluid and IgG-Fc receptor in the stria vascularis of the ordinary guinea pig.

Prospectively studying the possible autoimmune cause in ten patients with Meniere's disease, Hughes et al[19] found one of the patients had raised CIC levels by the cryoprecipitation assay technique. Brookes[10] reported the results of immune activity assessment in Meniere's disease. Thirty-six (54.5%) of his 66 patients with Meniere's disease were found to have significantly raised CIC levels by the PEG precipitation test. This high incidence was interpreted to be due to the different assay techniques employed or possibly due to the fact that the patients in his study were almost exclusively secondary referrals with relatively severe symptoms.[10] In the present study, using the same technique, we found that 32.2% of our patients with Meniere's disease had raised CIC levels (Fig 2). It also was found that more patients with bilateral hearing loss had raised CIC levels than those with unilateral hearing loss ($p < .005$), and the degree of hearing loss seemed to parallel the number of patients with raised CIC levels (Table 1).

Medium-sized immune complexes can remain in the circulation for a long period. Once deposited in the tissues, they will react with the complements and attract polymorphonuclear leukocytes, which infiltrate the vessel walls and discharge lysosomal enzymes. The glomerular capillary wall is one of the most frequent depositing sites. It has been shown that similarities exist between the stria vascularis and the glomerular capillaries in ultrastructure, physiologic function, and antigenicity.[20,21] Harada et al[18] demonstrated the presence of IgG-Fc receptor in the stria vascularis by the fluorescent antibody method. Hence, the stria vascularis is pos-

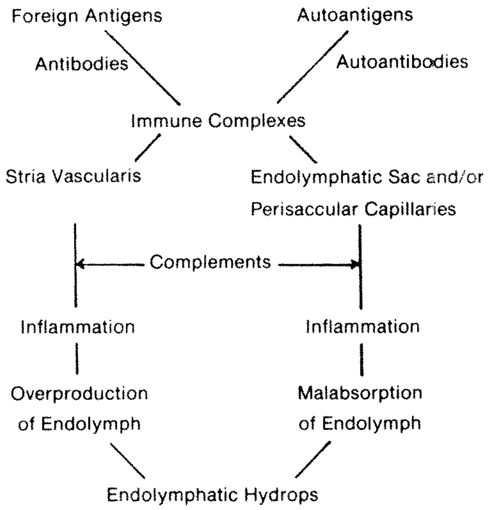

Fig 3. Possible mechanisms of immune complex-mediated endolymphatic hydrops.

sibly the site for deposition of CICs in the inner ear. Another possible site for deposition of immune complexes formed in situ is the endolymphatic sac. Recent evidence shows that the endolymphatic sac acts in the inner ear as an immunodefensive system[22] in which immunoglobulins may be locally produced.[23] Sawada et al[24] induced endolymphatic hydrops in systemically sensitized guinea pigs by introducing horseradish peroxidase into the endolymphatic sacs. Histologic study showed that the endolymphatic sacs of the affected guinea pigs were packed with soft granulation tissue, and showed IgG and C3 deposition in the challenged endolymphatic sacs. Thus, we tentatively presumed that some of the patients with Meniere's disease had an immune-complex-mediated type III allergy cause. The simplified mechanisms are shown in Fig 3.

It is obvious that further research should be carried out on direct evidence of deposition of immune complexes in the inner ears of Meniere's patients, the nature of the complexed antigens, and the role autoimmune reaction plays in the pathogenesis of endolymphatic hydrops.

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SENSITIVITY AND SPECIFICITY OF THE HEAD-SHAKING TEST FOR DETECTING VESTIBULAR SYSTEM ABNORMALITIES

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The head-shaking nystagmus (HSN) test has been reported to be a sensitive screening test for the presence of peripheral and central vestibular system disease. Previous investigations have utilized few subjects who were drawn from well-defined patient populations. The purpose of the present investigation was twofold: first, to determine the prevalence of HSN in a large unselected population of dizzy patients seen in an otology and neurotology practice, and second, to determine the sensitivity and specificity of this evaluation in the detection of vestibular system abnormalities as reflected by results of electronystagmography and rotary chair testing. The results of the investigation have suggested that the HSN test has a 27% sensitivity and an 85% specificity. The HSN test yields an acceptable number of false positives (15%) and an unacceptably large number of false negatives (73%).

KEY WORDS — dizziness, electronystagmography, head-shaking test, nystagmus.

INTRODUCTION

The head-shaking nystagmus (HSN) test has been reported to be a simple screening evaluation for peripheral vestibular system disease. The examination as originally described by Kamei et al[1] requires that the patient shake his or her head 30 times 1) in the horizontal plane, bent forward 30°, 2) in the horizontal plane, positioned normally, 3) in the coronal plane, and 4) in the sagittal plane. The examination as recently described by Hain et al[2] requires that the patient shake his or her head rapidly in a sinusoidal manner at a frequency of 2 c/s (minimum) for at least 20 cycles. In this manner, subjects are able to attain peak head velocities of 450°/s to 500°/s.[2] The test may be administered in complete darkness with the patient wearing search coils that are placed on the corneas.[2] Alternately, the test may be administered in a darkened room, with the patient wearing Frenzel lenses and utilizing electronystagmographic (ENG) instrumentation for recording eye movements.[3,4] The patient is requested to stop shaking his or her head after 20 to 30 seconds, and the eye movements, if any, are observed for a period of 30 seconds. Following this maneuver, three types of eye movements have been documented. A nystagmus with a predominate horizontal component and a fast phase directed toward the intact end organ has been observed immediately following the head-shake,[2,3] and has been termed "deficiency-type nystagmus."[5] A second type of HSN, called "recovery nystagmus," has been reported.[3,5] This nystagmus, directed toward the affected side, occurs following a 20-second latent period after the head-shaking has ceased. Finally, a biphasic HSN has been documented in patients with peripheral vestibular deficits, and is a combination of the latter two types.[5]

Application of the HSN test to clinical samples has been limited. Kamei and Kornhuber[3] reported the absence of HSN in their normal subjects; however, HSN was present in 25% of their patients with central nervous system disease (68% of these patients carried diagnoses of multiple sclerosis). Hain et al[2] reported the presence of HSN in 100% of their patients with peripheral vestibular system disease (six subjects). The purpose of the present investigation was to determine the sensitivity and specificity of this simple screening test by using a broad sample of dizzy patients presenting to an otology practice.

METHODS

The subjects were 116 consecutive dizzy patients seen for balance function testing. The test battery consisted of the HSN test, the conventional ENG test battery, and rotary chair testing. The ENG test battery included conventional tests for gaze-evoked nystagmus; pursuit; saccadic and optokinetic subsystem disease; spontaneous, position-induced, and positioning nystagmus; and alternate binaural bithermal caloric testing. Rotary chair testing (Neurokinetics, model 1010) was conducted over a frequency range including 0.01, 0.02, 0.04, 0.08, and 0.16 Hz (maximum velocity, 100°/s; maximum acceleration, 50°/s^2). The HSN test was conducted prior to the ENG examination. Surface electrodes were placed bitemporally and above and below the eye with better corrected vision. Calibration was performed by having the patients fixate 10° horizontal and vertical targets. Following calibration, patients were asked to close their eyes and shake their heads rapidly left-right in a sinusoidal manner (approximately 2 Hz) in a darkened room. The patients were instructed to stop shaking their heads after 30 seconds, at which time Frenzel lenses were placed over their eyes. Subsequently, the patients were directed to open their eyes and stare straight

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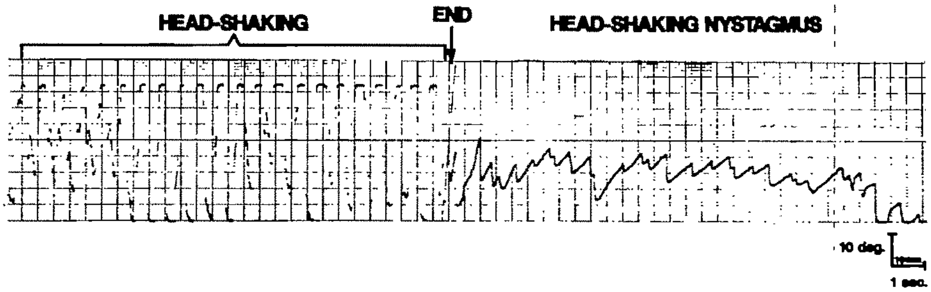

Head-shaking nystagmus obtained from subject in present investigation. Slow-phase eye velocity of this left-beating nystagmus was 90°/s (measurement technique described in text). It occurred without latent period and had duration of 15 seconds. This was most pronounced head-shaking nystagmus observed among subject group.

ahead. Electro-oculographic recordings were conducted during the head-shaking and for 30 seconds after the eyes were opened.

Results of HSN testing, the conventional ENG, and rotary chair testing were tabulated. The ENG results were considered abnormal if patients showed a gaze-evoked nystagmus, significant position-induced nystagmus, or a unilateral weakness on caloric testing. A spontaneous nystagmus in isolation was not considered abnormal in the absence of a significant unilateral weakness. Similarly, a directional preponderance was not considered abnormal if it was the sole positive finding in the ENG–rotary chair test battery. A significant positional nystagmus was operationally defined as a nystagmus exceeding 6°/s that was present in the majority of three positions. The positions included supine, body-right head-hanging, and body-left head-hanging. The ENG was also considered abnormal if a patient showed benign paroxysmal positional vertigo on Dix-Hallpike positioning.

Rotary chair testing results were considered abnormal if calculations of compensatory eye movement phase, spectral purity, or asymmetry exceeded two standard deviation upper limits of normal for two or more adjacent frequencies in the presence of normal vestibulo-ocular reflex gain. The HSN was quantified according to its maximum slow-phase eye velocity (SPEV), latency, and duration.

RESULTS

A total of 116 examinations were conducted. On 51 of these examinations (44%) abnormalities were found on caloric (ie, unilateral weakness) and/or rotary chair testing (ie, abnormal phase or asymmetry). Twenty-four of 116 patients showed HSN. This finding suggests a 21% prevalence of HSN in the population of dizzy patients that present to ear, nose, and throat physicians in a tertiary-care hospital setting. The HSN observed was primarily horizontal in direction, although two isolated instances of oblique nystagmus were seen as well. The fast phase of the HSN beat in the direction opposite the caloric unilateral weakness or rotational asymmetry in 21 instances (88%). On two occasions (8%) the fast phase of the nystagmus beat toward the impaired ear as indicated by asymmetries on caloric testing (eg, unilateral weakness) and/or rotary chair testing. For one subject (4%) it was difficult to determine the level of agreement between the results of caloric testing and the HSN test. This subject showed a caloric inversion[6] (ie, entire caloric response beating in the direction opposite to that expected) for all irrigations and showed no HSN.

The HSN occurred with a minimal latency (mean latency = 630 milliseconds; SD = 770 milliseconds) following cessation of head movement. The group mean maximum SPEV, measured as the average of the first two nystagmus beats upon eye-opening, was 12.40°/s (SD = 21.93°/s) and ranged from 2°/s to 90°/s. The Figure illustrates the HSN observed in a patient whose HSN SPEV reached 90°/s. If the latter subject was removed from this sample, the group mean maximum SPEV was 6.86°/s (SD = 4.66°/s). The duration of the HSN varied greatly among the subjects. The group mean duration of the HSN was 7.03 seconds (SD = 5.53 seconds), ranging from 2 to 17 seconds.

The HSN occurred in the presence of abnormal ENG and/or rotary chair test results 14 times (27% sensitivity). The HSN was observed in the absence of supportive ENG and/or rotary chair abnormalities in 10 instances (15% false positives). The ENG and/or rotary chair test results were abnormal without the occurrence of HSN in 37 subjects (73% false negatives). Finally, there were 55 instances wherein both ENG and/or rotary chair testing results were normal and there was an absence of HSN (85% specificity).

DISCUSSION

The mechanism of HSN is believed to involve the central velocity storage mechanism of the central vestibular system.[2,7,8] Rapid (ie, high-velocity) sinusoidal head movements cause asymmetries in the velocity storage mechanism. Excitatory activity elicited by rotations toward the intact ear is greater than the excitatory activity elicited by head rotations toward the impaired ear. This asymmetry in activity accumulates over the time of head-shaking, and the amount accumulated is dependent upon the degree of asymmetry in the sensitivity of the homologous end organs (ie, the horizontal semicircular canals for left-right head movements). When the head-shaking is stopped, the stored activity gradually discharges through the vestibulo-ocular reflex pathway. This usually results in a nystagmus with a fast phase directed toward the healthy ear.

The HSN test has been reported to be a sensitive screening test for detecting peripheral and central vestibular system disease. Previous investigations have been conducted on patients with well-defined diseases[3] or unilateral peripheral vestibular system disease.[2] Kamei et al[1] documented the presence of HSN in 86% of their dizzy patients. Kamei and Kornhuber[3] reported that 25% of their patients with central nervous system disease ($n = 60$) had HSN. This heterogeneous sample included patients with multiple sclerosis, cerebrovascular accidents, brain tumors, cerebral contusions, cerebrovascular insufficiency, spinocerebellar degeneration, and hereditary cerebellar atrophy, and one patient seen postoperatively following removal of a cerebellar tumor. The duration of HSN obtained from these patients ranged from 5 to 15 seconds. The authors did not report the distribution of HSN within each patient group. It is noteworthy that only two normal subjects showed HSN, although the nystagmus SPEV was reported to be less than 0.2°/s.

Recently, Takahashi[9] reported the results of HSN in 19 patients, 16 of whom had a unilateral peripheral vestibular system disorder. The investigator reported that in 19% of the cases ($n = 3$) the HSN showed an initial fast phase directed toward the impaired ear. In 68% of the cases ($n = 13$) the HSN showed a fast phase directed toward the healthy ear.

Hain et al[2] reported that 100% ($n = 6$) of their patients with unilateral losses of peripheral vestibular system function showed HSN. Five of these patients were seen postoperatively following the removal of acoustic neuromas, while the sixth patient had a labyrinthectomy for the treatment of Meniere's syndrome 10 years prior to the study. In four subjects, caloric responses were absent on the side of the lesion, and in one subject, caloric responses were depressed bilaterally. Caloric testing could not be performed in one patient. The HSN seen in these patients had a predominate horizontal component with the fast phase directed toward the healthy ear. One third of these patients showed an associated vertical down-beating component with a SPEV that exceeded 2°/s. The mean horizontal SPEV was 12.4°/s ($SD = 9.8°/s$), ranging from 3.8°/s to 30.5°/s. The authors reported the absence of a latent period between the end of head-shaking and the HSN. The authors did not report the duration of the HSN, but instead reported the time constant of the HSN to be 5.1 seconds ($SD = 3.4°/s$). Given the time constant (ie, the time required for the nystagmus SPEV to decline to 33% of its original velocity on eye-opening following head-shaking), one can extrapolate the duration of the HSN to be 7.65 seconds on the average. Contrary to the observations of Kamei and Kornhuber,[3] Hain et al[2] reported the presence of HSN with an SPEV exceeding 2°/s in 57% of their normal subjects ($n = 7$). It should be noted that Hain et al[2] used search coil technology instead of electro-oculography to record the HSN.

Previous investigations of patients with peripheral vestibular system disease have involved only patients with complete losses of vestibular system function. For example, Hain et al[2] indicated that the HSN test performed postoperatively was abnormal in five patients with acoustic tumors and in one patient following a unilateral labyrinthectomy. Four subjects had profound asymmetries on caloric testing. One subject had a bilateral loss of caloric responses. Contrary to the latter investigation, our sample was not limited to patients with unilateral vestibular paralysis, but included patients with various degrees of vestibular system disease as represented by results of caloric and rotary chair testing. Given the present hypotheses regarding the mechanisms underlying the generation of HSN,[7,8] it is reasonable to assume that lesser asymmetries in peripheral function would make the presence of HSN less likely. This might have accounted for the high false-negative rate (73%) observed in the present sample.

The present results are in partial agreement with those of previous investigators. The mean SPEV of the HSN observed in the present study was 12.4°/s, identical to the mean value reported by Hain et al.[2] The mean duration of the HSN (ie, measured from onset to threshold of visibility) was 7.03 seconds. This value corresponds well with the extrapolated value of 7.65 seconds from the Hain et al[2] study. In accordance with Hain et al,[2] a latent period between the end of head-shaking and the onset of HSN was not observed in our sample.

Although the HSN test has been regarded as a sensitive examination for detecting vestibular system abnormalities, the present study provided evidence to the contrary. We chose an unselected group of dizzy patients to determine whether the HSN test could be used to screen for vestibular system disease in a busy clinical practice. The sensitivity and specificity of the HSN test were found to be 27% and 85%, respectively, suggesting that the procedure is a poor predictor of vestibular system disease using caloric and/or rotary chair findings as external criterion validation. It is suggested that the poor intertest agreement may have occurred because the HSN test evaluates the upper end of the frequency range, which is not measured with conventional caloric (ie, low-frequency) or rotary chair (ie, low- and middle-frequency) stimulation.

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NASOPHARYNGEAL MASS: A MANIFESTATION OF INFLAMMATORY OTOLOGIC DISEASE

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A nasopharyngeal mass with cranial neuropathies usually indicates an advanced neoplastic process. We present three patients with these findings and concurrent invasive *Pseudomonas* otitis in whom repeated nasopharyngeal biopsies were negative for tumor. All of the nasopharyngeal masses resolved following treatment of the otitis. Mechanisms of disease spread from the temporal bone to the nasopharynx are discussed. Clinicians may choose to modify diagnostic and therapeutic approaches to the nasopharyngeal mass in patients with concurrent invasive otologic disease.

KEY WORDS — mastoiditis, nasopharyngeal diseases, nasopharynx, otitis, otitis externa, *Pseudomonas aeruginosa*.

INTRODUCTION

The principle that a nasopharyngeal disorder can result in otologic disease through eustachian tube obstruction is a basic tenet of otolaryngology. The resident is taught that unilateral serous otitis media in an adult may be the presenting sign of a nasopharyngeal mass. The converse principle, that an otologic disorder may produce nasopharyngeal disease, is not well recognized. A nasopharyngeal mass in the patient with a chronically infected ear can be a diagnostic and therapeutic challenge. Three such cases are described that illustrate this important clinical relationship.

CASE REPORTS

Case 1. A 64-year-old man presented with a 3-month history of left otalgia and facial pain. Examination revealed left serous otitis media with a 20-dB conductive hearing loss. A tympanostomy tube was placed in the left ear, and the patient was given oral antibiotics. A computed tomographic (CT) scan demonstrated a left nasopharyngeal mass (Fig 1), as well as a soft tissue density filling the left mastoid cells consistent with mastoiditis. Nasopharyngeal biopsy showed chronic inflammatory tissue. Both middle ear and nasopharyngeal cultures were positive for *Pseudomonas aeruginosa*. Over the ensuing 3 weeks a left abducens nerve paralysis developed; two additional nasopharyngeal biopsies were again negative for tumor. The patient's facial pain improved with a 2-week course of intravenous clindamycin phosphate and netilmycin sulfate for presumed subacute petrous apicitis. The abducens paralysis, otalgia, and nasopharyngeal mass resolved over the following 3 months.

Case 2. A 70-year-old diabetic woman presented with a 2-week history of left ear pain and drainage unresponsive to oral antibiotics. Examination revealed a central perforation of the left tympanic membrane with purulent debris in the external auditory canal. No granulation tissue was seen. An ear culture grew *P aeruginosa.* A CT scan revealed left mastoid clouding. The patient's symptoms resolved following a 2-week course of intravenous tobramycin sulfate and ticarcillin disodium. One month later she returned with a left facial paralysis and otalgia. On examination there was a dry tympanic membrane perforation with no evidence of granulation tissue. Repeat CT scan revealed a nasopharyngeal mass (Fig 2) with bony erosion of the petrous apex. Nasopharyngeal biopsy showed acute and chronic inflammation. A nasopharyngeal culture grew *P aeruginosa.* After beginning a second course of ticarcillin and tobramycin, she developed dys-

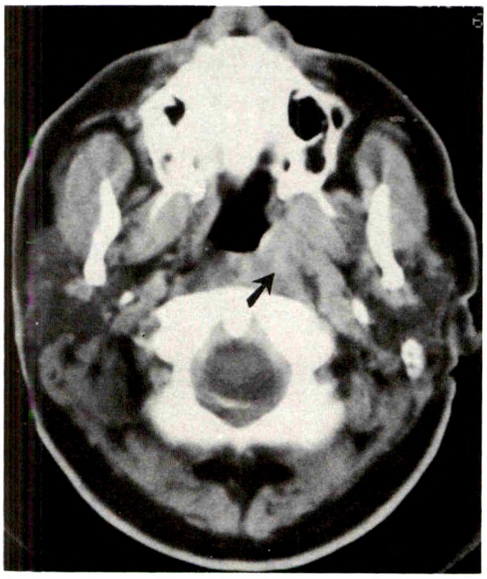

Fig 1. (Case 1) Computed tomograph showing left nasopharyngeal mass (arrow) with loss of pharyngobasilar and deep fascial planes.

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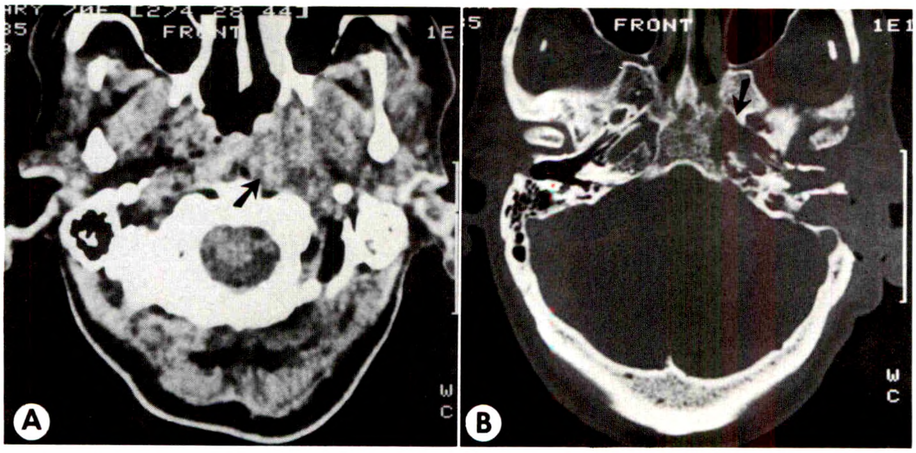

Fig 2. (Case 2) Computed tomographs showing A) left nasopharyngeal mass (arrow) with loss of fascial planes and B) bony erosion of left petrous apex with partial destruction of carotid canal (arrow).

phagia and hoarseness. Examination showed a new left true vocal cord paralysis with deficits of cranial nerves IX, X, and XII. A second nasopharyngeal biopsy was also negative for tumor. A radical mastoidectomy was performed, revealing extensive granulation tissue within the middle ear and mastoid. Her otalgia initially abated and then recurred over the following 2 weeks while she was still taking intravenous antibiotics. A subtotal exenteration of petrous apex cells was performed on the fourth week of hospitalization. Within 1 month there was complete resolution of her otalgia and paralysis of cranial nerves IX, X, and XII; however, her facial paralysis persisted.

Case 3. A 75-year-old diabetic man with a 1-month history of right otalgia and otorrhea presented with a new onset of right facial paralysis. Examination revealed an inflamed tympanic membrane with granulation tissue and purulent discharge in the right external auditory canal. A CT scan showed right mastoid clouding. A myringotomy yielded purulent material that grew *P aeruginosa.* The facial paralysis resolved after 2 weeks of intravenous ticarcillin disodium and tobramycin sulfate. The patient was discharged with planned interval mastoidectomy; however, he was readmitted 1 month later with right otalgia and positional unsteadiness. A radical mastoidectomy was performed, revealing a dehiscent facial nerve canal with extensive middle ear granulation tissue and cochlear erosion. His unsteadiness had resolved by the time of discharge 2 weeks later. The following month he was readmitted with recurrent otalgia and a new paralysis of cranial nerves X and XII. A CT scan revealed a right nasopharyngeal mass with bony erosion in the jugular fossa (Fig 3). A nasopharyngeal biopsy showed only acute and chronic inflammation. A nasopharyngeal culture was positive for *P aeruginosa.* The patient underwent transmastoid exploration of the skull base, in which necrotic bone was found at the jugular bulb. Microscopic examination demonstrated osteomyelitis. After 8 weeks of intravenous tobramycin and ceftazidime, there was complete resolution of cranial neuropathies, the nasopharyngeal mass, and otalgia.

DISCUSSION

A nasopharyngeal mass with cranial neuropathies usually indicates an advanced neoplastic process. In the patient with concurrent otologic disease, however, such a mass may well represent an inflammatory response to an adjacent infectious process. In the three patients presented above, nasopharyngeal masses represented extension from infection within the temporal bone. These masses were negative for tumor on biopsy and resolved with treatment of a concurrent invasive *Pseudomonas* otitis — subacute mastoiditis leading to Gradenigo's syndrome (case 1), chronic mastoiditis evolving to petrous apicitis (case 2), and mastoiditis with malignant exter-

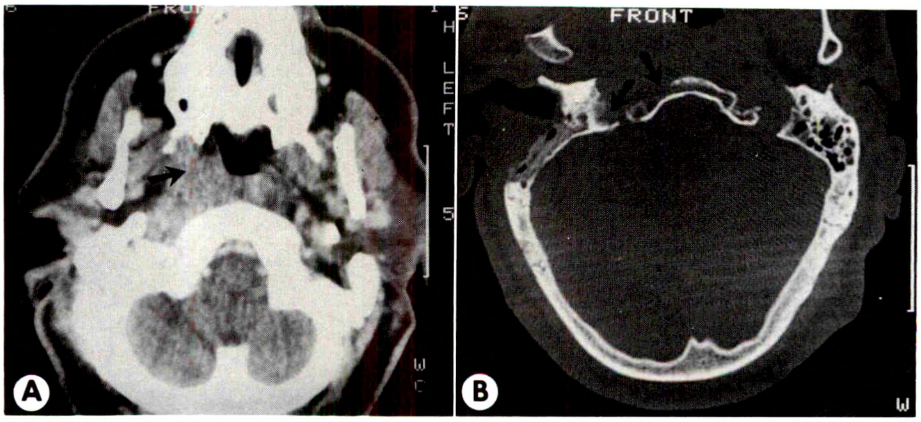

Fig 3. (Case 3) Computed tomographs showing A) right nasopharyngeal mass (arrow) with loss of fascial planes and B) bony erosion involving right jugular foramen and clivus (arrows).

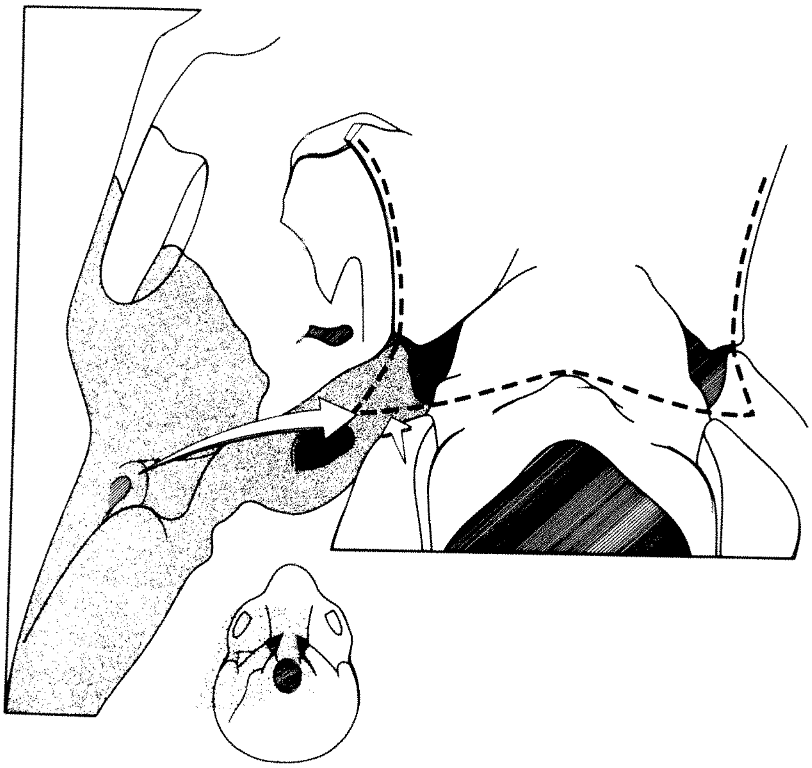

Fig 4. Base of skull view demonstrating anatomic proximity of temporal bone and nasopharynx. Note how pharyngobasilar fascia (dashed line) that outlines nasopharynx crosses petrous portion of temporal bone (short arrow), allowing for direct spread of infection from petrous apex to nasopharynx. Long arrow — alternative path of infectious spread from external auditory canal or mastoid via soft tissues along skull base to pharyngeal structures.

nal otitis (case 3). In each case *P aeruginosa* was cultured from both the ear and the nasopharynx.

The proximity of the nasopharynx to the adjacent petrous portion of the temporal bone allows for contiguous spread of otologic infection to the pharyngeal tissues. The integrity of the nasopharyngeal wall is maintained by the pharyngobasilar fascia, which is anchored to the skull base at the pharyngeal tubercle in the midline and extends laterally across the petrous portion of the temporal bone in front of the carotid canals (Fig 4). Anteriorly, it attaches to the medial pterygoid plates. An infectious otologic process that extends beyond the confines of the temporal bone at the petrous apex is already within the boundaries of the nasopharynx. Indeed, bony erosion of the petrous apex, as well as a nasopharyngeal mass, was evident on CT scan in case 2. In case 1 no such erosion was seen; however, the patient did have mastoiditis with an abducens nerve paralysis, and the presumptive diagnosis was petrous apicitis.

Alternatively, infection from the nonpetrous portion of the temporal bone can spread to the nasopharynx by extension along the skull base. Such a mechanism of spread is classic for malignant otitis externa, which follows fascial and vascular planes as it involves cranial nerves along the skull base.[1] The clinical presentation of case 3, an elderly diabetic patient with a facial paralysis and granulation tissue in the external auditory canal, resembles that of malignant otitis externa as described by Chandler[2]; however, our patient also presented with a concurrent purulent middle ear effusion. In retrospect, a 6-week course of intravenous antibiotics would have been appropriate. Adequate initial therapy might have altered the necessity for further treatment. As his disease progressed and paralysis of cranial nerves X and XII evolved, he eventually developed erosion of the jugular foramen, as well as a nasopharyngeal mass.

If the *Pseudomonas* infection had spread along soft tissues in an inferior or lateral direction, a retropharyngeal or lateral pharyngeal mass could have developed. Dinapoli and Thomas[3] described a patient with malignant otitis externa and cranial neuropathies who developed a lateral pharyngeal mass. As in our cases, multiple biopsies of this mass were negative for neoplasm. Allam and Schuknecht[4] examined the temporal bones of an individual with chronic suppurative petrositis and cranial neuropathies and found abscesses in the peritubal, epidural, and retropharyngeal regions. Nadol[1] described an additional patient with malignant otitis externa and parapharyngeal edema who was found to have a retropharyngeal abscess at autopsy.

Dogma dictates the need for a biopsy to exclude neoplasm in the presence of a nasopharyngeal mass and otologic disease, particularly in the adult with unilateral serous otitis media. However, the repeated nasopharyngeal biopsies performed in cases 1 and 3 might have been avoided had there been greater awareness of the relationship between invasive *Pseudomonas* otitis and inflammatory parapharyngeal masses. Furthermore, nasopharyngeal carcinomas most commonly affect cranial nerve V, followed by nerves VI, III, and IV.[5] Only advanced tumors will cause neuropathies of the lower cranial nerves VII, IX, X, XI, and XII as occurred in our patients. Our experience suggests that a nasopharyngeal mass that develops in the setting of a concurrent invasive *Pseudomonas* otitis can be initially managed by treatment of the otologic disease.

In all three of our cases the nasopharyngeal mass was an unexpected finding on CT scan. In a paper on CT and magnetic resonance imaging for malignant otitis externa, Gherini et al[6] describe the associated finding of soft tissue swelling in the nasopharynx with obliteration of prevertebral and pharyngobasilar fascial planes. With increased utilization and resolution of noninvasive imaging in patients with otologic diseases, the likelihood of finding such masses can be expected to increase. Clinicians who are aware of this association between pharyngeal masses and invasive otitis will be able to make more knowledgeable clinical decisions.

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THE DEAFNESS RESEARCH FOUNDATION
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CARCINOID TUMORS OF THE MIDDLE EAR

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Carcinoid tumors of the middle ear are rare lesions that represent a class within the spectrum of adenomatous neoplasms. We present four cases that were diagnosed and treated at our institution since 1973, and review the pool of 12 cases in regard to their presentation, symptomatology, physical examination, audiometric and radiographic evaluations, operative procedure and findings, histopathology, and postoperative course. Successful treatment of these low-grade malignancies requires complete excision of the tumor mass, along with the ossicles if they are involved with disease, in order to prevent local recurrence. Although locally invasive, these tumors have a low propensity for distant metastasis. The diagnosis of carcinoid tumor should be considered in all cases of adenomatous neoplasms of the middle ear and mastoid.

KEY WORDS — carcinoid tumor, ear neoplasms, middle ear.

Carcinoid tumors of the middle ear are rare neoplasms. The first such case was reported in 1980 by Murphy et al,[1] who noted its microscopic similarity to adenomatous tumors of the middle ear. They suggested that carcinoid tumors should be suspected in cases of adenomatous lesions of the middle ear in which the histologic appearance shows a trabecular pattern. They recommended argyrophil staining and electron microscopy as two components in the pathologic diagnosis of these tumors.

Since this initial report by Murphy et al, seven additional cases have been reported.[2-7] We present here clinical data from four additional cases of carcinoid tumors of the middle ear seen at our institution, two of which were initially diagnosed as adenocarcinoma and adenoid cystic carcinoma. We also discuss the presentation, behavior, clinical appearance, and histology of these unusual lesions. Finally, we present recommendations in the treatment of these rare tumors.

CASE REPORTS

Case 1. A 26-year-old man initially developed a sensation of blockage in his right ear in 1984, which progressed over several months with the gradual development of otalgia. Examination by an otolaryngologist demonstrated the presence of a mass in the middle ear that on biopsy was described as an "adenocarcinoid tumor of the middle ear." He was referred to an otologist, who performed a transcanal tympanotomy and excision of the tumor. Following the operation, the patient noted a profound sensorineural hearing loss in the operated ear with accompanying dizziness. A follow-up computed tomographic scan 1 year later suggested recurrence of the tumor, but repeat exploration failed to demonstrate recurrent disease. The patient was well until September 1987, when he began to have recurrent right otalgia accompanied by worsening tinnitus. A CT scan was again performed, which demonstrated a recurrent mass in the right middle ear, extending from the malleus handle to the promontory, without evidence of bony destruction. He was referred for further evaluation and treatment.

On examination, the patient had an area on the posterior tympanic membrane that appeared tympanosclerotic, corresponding precisely to the location of the mass on CT scan. He had no useful hearing in the right ear, with normal hearing on the left. His facial nerve function was normal. The remainder of the findings on head and neck examination were unremarkable, with the exception of mild oral candidiasis from recent antibiotic therapy. Audiometry demonstrated no hearing in the right ear.

In March 1988, the patient underwent an exploratory tympanotomy, postauricular canalplasty and meatoplasty, anterior atticotomy, and total tympanic membrane replacement, with excision of tumor from the middle ear. At operation, the patient had two whitish, avascular, noninvasive soft tissue masses, one of the mesotympanum, and one of the epitympanum attached to the ossicular mucosa. The incus was partially eroded and was removed. The tumors were easily dissected and excised. The facial nerve was not involved with tumor. Delayed skin grafting to the canal was performed 1 month following the operation.

Histopathologic examination of the specimen with H & E demonstrated a trabecular network of branching and anastomosing cords, with glandlike structures (see Figure, A). Cytoplasm was lightly eosinophilic with a fine, granular texture. Grimelius staining demonstrated darkly staining cytoplas-

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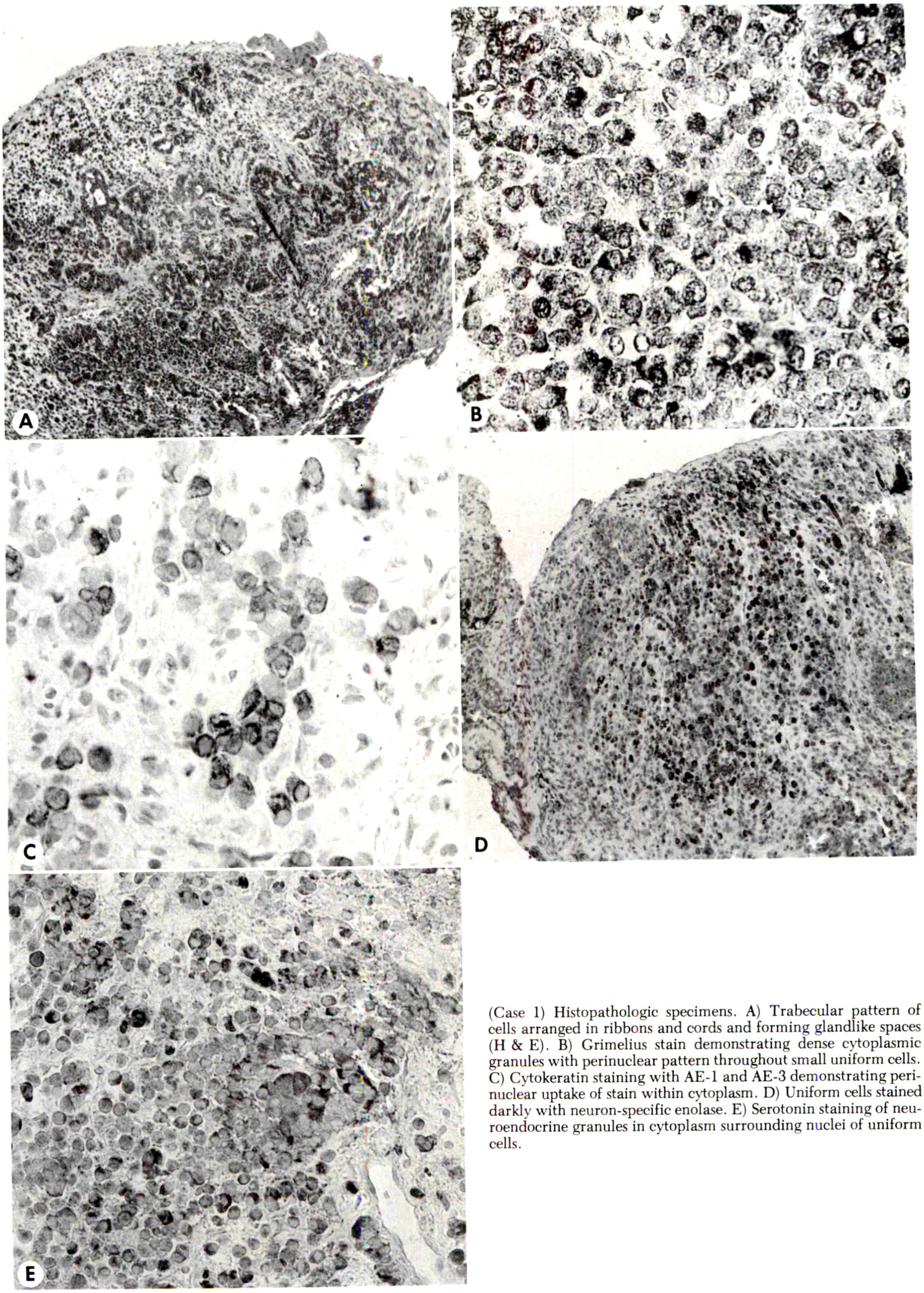

(Case 1) Histopathologic specimens. A) Trabecular pattern of cells arranged in ribbons and cords and forming glandlike spaces (H & E). B) Grimelius stain demonstrating dense cytoplasmic granules with perinuclear pattern throughout small uniform cells. C) Cytokeratin staining with AE-1 and AE-3 demonstrating perinuclear uptake of stain within cytoplasm. D) Uniform cells stained darkly with neuron-specific enolase. E) Serotonin staining of neuroendocrine granules in cytoplasm surrounding nuclei of uniform cells.

mic granules in a perinuclear pattern (see Figure, B), confirming the argyrophilic nature of the tumor. Immunohistochemistry demonstrated positive cytokeratin staining with combined AE-1 and AE-3 antiserum (see Figure, C), as well as positive cytoplasmic granules with both neuron-specific enolase (see Figure, D) and serotonin (see Figure, E). Electron microscopic examination showed densely staining neurosecretory granules. These findings confirmed the neuroendocrine nature of the lesion and were consistent with a diagnosis of carcinoid tumor.

Case 2. A 49-year-old woman noted a sensation of blockage in her right ear that developed over a period of 1 year in 1974. She was examined by an otolaryngologist and was noted at that time to have a reddish mass behind the posterosuperior portion of the tympanic membrane. Audiometry demonstrated a 10-dB air-bone gap in the right ear.

In May 1975, a right exploratory tympanotomy was performed that demonstrated neoplastic tissue in the posterior mesotympanum, mastoid antrum, and medial part of the central mastoid tract. A radical tympanomastoidectomy was then performed. Because of its intimate involvement with tumor, the stapes was removed. All tumor was exenterated, and the mastoid obliterated. Grafts of fibrous tissue were placed in the mastoid and middle ear.

Histopathologic examination demonstrated a solid mass of fibrous tissue with islands of pleomorphic cells showing a strong tendency to glandular arrangement. The stapes suprastructure was encompassed by the tumor mass. Scattered throughout the specimen were small, cystic spaces. An initial diagnosis of low-grade adenoid cystic carcinoma was made. On the basis of this diagnosis of an aggressive neoplasm, the patient received 60 Gy of external beam irradiation to the right middle ear and mastoid. The patient is without recurrence of her disease to date. Reexamination of the initial pathology slides demonstrated a trabecular, glandular pattern of small cells, which on review is felt to be more consistent with the diagnosis of carcinoid tumor than with that of adenoid cystic carcinoma.

Case 3. An 18-year-old boy noted hearing loss in his right ear at the time of an upper respiratory tract infection in 1972. He was treated with antibiotics and a ventilation tube by an otolaryngologist without relief of his hearing loss. He was then referred to our institution for further evaluation and treatment. Examination at that time demonstrated a red, bulging tympanic membrane without evidence of either acute infection or serous fluid. Audiometry revealed a 40- to 50-dB up-sloping conductive hearing loss.

An exploratory tympanotomy and biopsy were performed in August 1973, and a diagnosis of adenocarcinoma was returned. One week later the patient underwent a wide-field radical tympanomastoidectomy. Tumor mass was noted in the epitympanum and mesotympanum, invading the stapes and filling the obturator foramen. Once all disease had been exenterated, the tympanomastoid compartment was obliterated with abdominal fat.

Histopathology of the specimen demonstrated a highly cellular soft tissue mass consisting of small hyperchromatic cells arranged in nests and strands. Mitotic figures were rare. The diagnosis was modified at that time to low-grade adenoid cystic carcinoma of the middle ear. Once again, on the basis of this diagnosis, the patient received aggressive therapy in the form of 45 Gy of external beam irradiation. The patient continues to be free of disease. Current review of the pathology slides demonstrates a trabecular pattern of small cells with a definite tendency toward glandular arrangement. From our present knowledge of the spectrum of adenomatous neoplasms of the middle ear, the appearance of this tumor is now considered to be consistent with that of a carcinoid tumor.

Case 4. A 30-year-old man complained of a feeling of fullness in his right ear. He denied tinnitus, but did report slight intermittent pain. He presented to our department, where he was noted to have a well-demarcated whitish mass behind the right tympanic membrane. The mass was nonpulsatile and nonerythematous. Audiometry revealed a 10-dB air-bone gap in the right ear.

In September 1985 the patient underwent an exploratory tympanotomy and biopsy that revealed a large, whitish mass that filled the posterosuperior portion of the right middle ear space. The pathologic findings were interpreted as showing adenomatous tumor of the middle ear. Three days later the patient underwent a postauricular radical tympanomastoidectomy. At operation, the large mass described above was noted, with extensions into the facial recess, sinus tympani, epitympanum, aditus, and anterior part of the mastoid. The stapes was firmly embedded in the tumor mass and was removed. Once all tumor was exenterated, the middle ear and mastoid were obliterated with abdominal fat.

Histopathology demonstrated a trabecular, anastomosing pattern of small cells arranged in glandlike structures, raising the issue of carcinoid tumor. Special stains were done, and were positive for immunoperoxidase, neuron-specific enolase, and serotonin, confirming the neuroectodermal *differentiation* of the tumor. On the basis of the histopathologic appearance and the special stains, a diagnosis of carcinoid tumor was made. The patient underwent 45 Gy of postoperative radiation therapy, and is without recurrent disease.

COMMENT

A review of these 12 carcinoid tumors of the mid-

TABLE 1. REVIEW OF 12 CASES OF CARCINOIDS OF MIDDLE EAR

Study	*Age*	*Sex*	*Symptoms*	*Findings on Physical Examination*	*Audiogram Results*	*Presence of Carcinoid Syndrome*	*Radiographic Findings*
Murphy et al[1]	30	M	Severe HL	Intact TM, displaced laterally by soft tissue mass	Severe SNHL	No	Decreased aeration of mastoid with density in middle ear
Inouye et al[2]	35	F	Fullness, tinnitus, slight HL	Intact TM, mass in canal and middle ear	15 dB to 40 dB CHL	No	NR
Friedmann et al[3]	33	M	Progressive HL, transient VII palsy	Intact TM, no mass seen	NR	No	Tumor involving facial nerve
Manni et al[4]	51	F	Decreased hearing	Erythema of TM	20 dB CHL	No	Decreased aeration of mastoid
Tange et al[5]	53	M	Progressive HL over 6 months	Intact TM, bulging superiorly with erythema	Sloping 25 to 30 dB SNHL	No	No tumor on plain films
Stanley et al[6] (case 1)	34	F	Fullness, HL	Bulging TM with pale mass in middle ear	35 dB CHL	No	No tumor on plain films
Stanley et al[6] (case 2)	21	M	Decreased hearing	Reddened TM with obscured landmarks	CHL	No	Infantile mastoid with decreased pneumatization
Sakurai et al[7]	43	F	Fullness, tinnitus, HL	Thickened TM, posterior erythema	Mild CHL	No	Soft tissue in mastoid, diffuse shadow in antrum
This study (case 1)	26	M	Blockage sensation in ear, pain	Intact TM, mass in middle ear	NR initially	No	Mass in middle ear, extending from malleus handle to promontory
This study (case 2)	49	F	Blockage sensation in ear	Reddish mass behind posterosuperior TM	10 dB CHL	No	No tumor on polytomography
This study (case 3)	18	M	HL	Bulging, red TM	40 to 50 dB CHL	No	Increased density in right epitympanum and mesotympanum
This study (case 4)	30	M	Fullness in ear	Well-demarcated whitish mass behind TM	10 dB CHL	No	Soft tissue mass in mastoid and middle ear

HL — hearing loss, TM — tympanic membrane, SNHL — sensorineural hearing loss, CHL — conductive hearing loss, NR — not recorded, NSG — neurosecretory granule.

dle ear demonstrates several important findings (Table 1).[1-7] Tumors are noted in both men and women, and present from the second through sixth decades. All 12 patients presented with ear blockage and hearing loss, usually conductive, although two patients had audiograms showing sensorineural losses. Tinnitus was reported in three patients, while one patient noted a transient facial paresis. On examination the tympanic membrane was generally intact, but often bulging laterally. In only five of these 12 cases was a middle ear mass actually seen on otoscopic examination, while in six other cases the drum was described as reddened or hyperemic. In the 12th case the mass was seen only on tomographic examination. None of the 12 patients demonstrated symptoms of the carcinoid syndrome.

At operation, the tumor was generally described as soft, white or pale, smooth and lobulated, and avascular, and in 11 cases it engulfed and surrounded the ossicles. In fact, its point of attachment in the middle ear often appeared to be the ossicular mucosa. The tumor was primarily found in the middle ear space, and extended into the mastoid in seven of 12 cases. In one case,[3] the mass was more yellow and enveloped the facial nerve, sparing the ossicles, and was described as a "mixed carcinoid tumor." In ten of the 12 cases, an initial tympanomastoidectomy was used to approach and exenterate the disease. In two cases,[5,6] the initial operation was conservative, involving tympanotomy and peeling of the tumor from the involved ossicles. In both of these patients the tumors recurred within 3 years, and subsequent exenterative operations were performed. No recurrences have been reported after the operations in which the affected ossicles were removed along with the tumor. In three patients cared for at this institution, postoperative radiotherapy was prescribed on the basis of the initial pathologic diagnosis. In two of these three patients, the initial histology was interpreted as showing an aggressive, invasive tumor with a high potential for a lethal outcome. On the basis of our current understanding of the pathologic condition and its implications, we now feel that radiotherapy is unnecessary in localized disease.

Histopathologic examination classically demonstrated ribbons and cords of cuboidal to columnar cells with a trabecular pattern. Cells were seen in small nests with anastomoses of cords and glandlike structures. Argyrophil staining was positive in eight of the ten cases sampled with the Grimelius reaction. Immunohistochemical stains were positive for cytokeratins AE-1 and AE-3, demonstrating the epithelial origin of carcinoid tumors. Stains for

TABLE 1 (continued). REVIEW OF 12 CASES OF CARCINOIDS OF MIDDLE EAR

Procedure	*Operative Findings*	*Histopathologic Findings*	*Grimelius Stain*	*Findings on Electron Microscopy*
Radical mastoidectomy	Soft mass in middle ear, into mastoid, involving ossicles	Trabecular, anastomosing cords with glandlike structures	+	NSGs
Tympanotomy, removed ossicles	Soft, white, fragile mass filling middle ear, into mastoid, involving ossicles	Trabecular, anastomosing cords with glandlike structures	+	NSGs
Radical mastoidectomy	Yellow mass enveloping facial nerve	Mixed pattern, tubular-trabecular ductal features with solid nests	+	NSGs
Radical mastoidectomy	Mass in middle ear	Ribbons and cords of small cells in cords and glandular patterns	+	NSGs
Radical mastoidectomy	Well-encapsulated, lobulated tumor involving ossicles	Cribriform, columnar/cuboidal cells, small nests, glands, cords	+	NSGs
Tympanomastoidectomy, type III	Pale, smooth, lobulated tumor in middle ear, into antrum, involving ossicles	Ribbons and cords of uniform columnar cells, trabeculae, and confluence of cords	–	NSGs
Tympanotomy, cleaned ossicles, recurred, then radical mastoidectomy	Pale, white, bulging tumor of fatlike tissue, attached to TM, involving ossicles	Ribbons and cords of uniform columnar cells, trabeculae, and confluence of cords	–	NSGs
Radical mastoidectomy, laser therapy	Yellow-white mass in attic, encasing ossicles	Uniform cuboidal to columnar cells forming solid, trabecular anastomosing cords	+	NSGs
Tympanotomy, excision, recurred, then atticotomy and tympanotomy	Two whitish, avascular, soft, noninvasive masses, in both mesotympanum and epitympanum	Trabecular, anastomosing cords with glandlike structures	+	NSGs
Radical tympanomastoidectomy, postoperative radiation therapy	Mass in mesotympanum, antrum, and central mastoid tract, involving stapes	Solid mass of fibrous tissue with islands of cells and glandlike structures and cystic spaces	NR	NR
Radical tympanomastoidectomy, postoperative radiation therapy	Mass in mesotympanum and epitympanum, into obturator foramen, surrounding stapes	Highly cellular soft tissue with nests and strands of small cells and glandlike arrangement	NR	NR
Radical tympanomastoidectomy, postoperative radiation therapy	Whitish mass in middle ear, extending into mastoid, embedded into stapes	Trabecular, anastomosing cords with glandlike structures	+	NR

serotonin and neuron-specific enolase were also positive, consistent with the neuroendocrine lineage of these tumors. Characteristic neurosecretory granules were present on electron microscopy in all nine cases so examined. In contrast, paragangliomas, adenoid cystic carcinomas, and adenocarcinomas do not stain with either the Grimelius reaction or with serotonin. In addition, while paragangliomas do demonstrate neurosecretory granules on electron microscopy, they are not shown with cytokeratin stains, since they are not of epithelial origin.[8] Table 2 presents a comparison of specific differential findings in this group of neoplasms.

Carcinoid tumors are unusual lesions that are often thought to be derived from the enterochromaffin or Kulchitsky's cells of the endocrine system.[9] These cells are widely distributed, although they have not been demonstrated specifically within the middle ear space. They have the capacity for uptake and decarboxylation of amine precursors, and are therefore termed as APUD cells. Their ability to synthesize, store, and release a variety of active peptide hormones is well recognized.[9] Kulchitsky's cells are demonstrated on electron microscopy to contain dense neurosecretory granules. The presence of these granules in adenomatous lesions of the middle ear strongly suggests the diagnosis of carcinoid tumor.

Carcinoid tumors have been classified according to their sites of origin as foregut, midgut, or hindgut lesions.[10] Since the tympanic cavity forms from the foregut entoderm of the first pharyngeal pouch,[11] it is reasonable to consider carcinoids of the middle ear as foregut tumors. Histologically, foregut carcinoids generally exhibit an argyrophil reaction only with the Grimelius method, and are often argentaffin-negative.[12] This fact is useful in their histopathologic examination and should be considered in all cases of suspected adenomatous tumors of the middle ear. In addition, foregut carcinoids generally produce only small amounts of peptide hormones, and therefore are usually systemically asymptomatic. The well-known "carcinoid syndrome" (flushing, wheezing, cramping, and diarrhea) is therefore absent in these lesions.[9] Clinically, foregut carcinoids, including those of the lung and bronchus, are slow-growing and relatively benign in their behavior, with a 5-year survival in localized disease of 96%.[13] In fact, carcinoid tumors of the lung were once described as "bronchial adenomas" because of their benign clinical behavior.

SUMMARY

Carcinoid tumors of the middle ear are rare, low-

TABLE 2. HISTOCHEMICAL AND ELECTRON MICROSCOPIC FEATURES OF MIDDLE EAR NEOPLASMS

Stain	*Carcinoid Tumor*	*Adenocarcinoma*	*Adenoid Cystic Carcinoma*	*Paraganglioma*
Grimelius	+	−	−	−
Serotonin	+	−	−	−
Neuron-specific enolase	+	−	+	+
Cytokeratins AE-1, AE-3	+	+	+	−
Neurosecretory granules (electron microscopy)	+	−	−	+

grade malignant neoplasms. They represent a class within the spectrum of adenomatous tumors whose clinical and histologic appearance can be easily confused with either benign adenomas or with highly aggressive carcinomas. They are, however, a distinct diagnostic entity that must be considered in the differential diagnosis of all adenomatous masses of the middle ear. These tumors are slow-growing, locally infiltrative, clinically benign lesions that are characteristically associated with and invade the ossicles. They present with ear blockage and progressive hearing loss without vestibular symptoms or evidence of the carcinoid syndrome. In only one case was there a transient facial weakness, but this "mixed carcinoid tumor," arising within a paraganglioma, was unlike the other 11 lesions in this review. Physical examination demonstrates an abnormal but intact tympanic membrane with either hyperemia or a frank middle ear mass. While routine radiographs may reveal no abnormalities, special procedures, especially CT scanning, may be useful in better delineating the mass and its extent. It is important to note that these radiographic studies uniformly fail to demonstrate any bony erosion or destruction.

Adequate treatment requires removal of the tumor along with the ossicles enveloped by the tumor in order to avoid recurrence. Extension into the mastoid requires tympanomastoidectomy, while isolated tympanic disease can be treated with tympanotomy and atticotomy as long as all tumor is removed along with the involved ossicles. Recurrence is unlikely with adequate local excision. While radiation therapy was used in several cases initially diagnosed as more aggressive lesions, our present understanding of the histopathology, behavior, and prognosis of these tumors suggests that radiation therapy is unnecessary in localized disease. We would therefore not recommend its use in well-circumscribed lesions. In tumors that are incompletely excised, or in those that have spread beyond the mastoid and middle ear, radiation therapy might play a role in management, although no such cases have yet been reported.

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ENDOTRACHEAL TUBE SAFETY WITH THE ERBIUM:YTTRIUM ALUMINUM GARNET LASER

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The erbium:yttrium aluminum garnet (Er:YAG) laser operates in the infrared spectrum at a wavelength of 2.94 μm. The absorption coefficient for water at this wavelength is approximately 10 times that of the carbon dioxide laser. It is anticipated that this laser will produce more precise surgical ablation with decreased surrounding tissue destruction. The results of impacting endotracheal tubes with the Er:YAG laser are presented. The CO2 laser was used as a reference. Metallic tape that was not perforated by the CO2 laser after 240 seconds of continuous exposure at 20 W was perforated by the Er:YAG laser with use of 15 pulses of 1 J per pulse. Silver foil tape with a Merocel lining was resistant to perforation by both the CO2 laser and the Er:YAG laser. As new laser wavelengths become available and are applicable to otolaryngology, modification of current safety standards will be necessary.

KEY WORDS — endotracheal tube, erbium:yttrium aluminum garnet laser, laser safety, lasers.

INTRODUCTION

The use of lasers in medicine and surgery has been well established during the last two decades. Lasers offer the surgeon precise ablation of tissue with minimal surrounding tissue injury. Other advantages include noncontact control of delivery, a dry field, and ability to deliver the energy to confined areas without the need for an open procedure. The specific tissue effects of laser energy are dependent on 1) wavelength of the laser, 2) optical absorptivity of tissue at a particular wavelength, 3) power density, 4) duration of the laser beam, and 5) volume of tissue treated (spot size). Presently, four surgical lasers of different wavelengths are used in otolaryngology–head and neck surgery: the carbon dioxide laser, the neodymium:yttrium aluminum garnet (Nd:YAG) laser, the argon laser, and the potassium-titanyl phosphate/532 laser. Each one of these lasers has specific advantages and disadvantages related to its wavelength, optical, and tissue interaction characteristics. Current laser research includes the development of new-wavelength lasers with optical and tissue interaction properties favorable to surgical applications. One such laser is the erbium:yttrium aluminum garnet (Er:YAG) laser, which operates in the infrared spectrum at a wavelength of 2.94 μm. The absorption coefficient for water at this wavelength is approximately 10 times that of the CO2 laser. It is anticipated that this laser will produce more precise surgical ablation with decreased surrounding tissue destruction.

This study was performed to investigate whether current safety precautions used to protect endotracheal tubes during use of surgical lasers would be adequate for the Er:YAG laser.

MATERIALS AND METHODS

The Sharplan 1040 CO2 laser, operating at a wavelength of 10.6 μm, was used in both the continuous and superpulsed modes. Power settings between 10 and 40 W were delivered at various time intervals and focused on endotracheal tubes wrapped with different protective tapes. The working spot size diameter was 0.4 mm. A solid-state Er:YAG laser operating at a wavelength of 2.94 μm was also used. The working spot size diameter was 0.6 mm. Multiple 1-J pulses were applied to endotracheal tubes wrapped with different protective tapes. Both lasers were focused with a 150-mm zinc-selenium lens.

Protective tape wrappings used were an aluminum tape (Mystic brand) and a Merocel sponge-padded silver tape (Laser Guard, Merocel Corp). These tapes were applied to polyvinyl chloride endotracheal tubes (Shiley) and placed in front of the laser light. A continuous flow of 100% oxygen was passed through the endotracheal tube, and fire ignition of the endotracheal tube was the end point.

RESULTS

Carbon Dioxide Laser. An unprotected endotracheal tube was perforated with a single pulse of 15

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VULNERABILITY OF ENDOTRACHEAL TUBES TO LASER ENERGY WITH USE OF SILVER VERSUS ALUMINUM PROTECTIVE TAPE

Endotracheal Tube	*Laser*	*Setting*	*Pulses or Time*	*Result*
No tape	CO_2	15 W	0.5 s	Perforated
Aluminum	CO_2	20 W	240.0 s	Intact
Silver	CO_2	20 W	180.0 s	Intact
No tape	Er:YAG	1 J	1 pulse	Perforated
Aluminum	Er:YAG	1 J	15 pulses	Perforated
Silver	Er:YAG	1 J	600 pulses	Intact

W with a 0.5-second exposure time (see Table). Both the aluminum and silver tapes protected the endotracheal tube from the CO_2 laser with both the continuous-wave and superpulsed outputs. The aluminum tape withstood a 20-W output for 240 seconds with no damage to the tape. The Merocel sponge silver tape received a 20-W output for 180 seconds with no damage to the tape. The average power density was 32 kW/cm^2.

Erbium:Yttrium Aluminum Garnet Laser. The unprotected endotracheal tube was perforated with a single 1-J pulse (see Table). The aluminum tape wrap was also perforated after 15 pulses with 1 J per pulse (Fig 1). The Merocel-padded silver tape withstood 600 pulses with 1 J per pulse with no evidence of damage to the silver tape. The Merocel sponge, however, was vaporized (Fig 2). The average power density was 700 W/cm^2.

DISCUSSION

The applications of lasers to biology and medicine have allowed significant improvements in endoscopic treatment of laryngeal and tracheal disorders. The use of the surgical laser has permitted more precise excision and ablation of tissue in areas to which access is limited. In the last 20 years, the treatment of acquired subglottic stenosis has changed from virtually all patients' requiring tracheotomy (with long-term mortality rates as high as 25% to 40%) to precise surgical excision of scar with the avoidance of tracheotomy or permitting early decannulation.[1-5]

Presently, the CO_2 and Nd:YAG lasers are among the most widely used lasers for otolaryngology–head and neck surgery; however, each suffers from distinct disadvantages. The CO_2 laser, while preferentially absorbed by water in biologic tissue, cannot be delivered through optical fibers. The Nd:YAG laser is capable of fiberoptic delivery; however, a large area of thermal injury beyond the intended target tissue limits its usefulness in microsurgical ablation of tissue.

The development of a prototype Er:YAG laser with a wavelength of 2.94 μm may herald an even more precise surgical tool. The absorption coefficient for water at a wavelength of 2.94 μm is 4,500 cm^{-1}.[6] The Er:YAG laser should be able to attain high power density within biologic tissues, affording a cleaner, more precise cut with less adjacent tissue injury. Because of its pulsed nature, the laser would also allow for tissue cooling between pulses, again decreasing the adjacent tissue injury. Studies by Esterowitz et al[6] using the Er:YAG laser on atheromatous plaques have demonstrated precise ablation with minimal surrounding tissue injury. Studies in our laboratory have demonstrated significantly less adjacent thermal injury when the Er:YAG laser is used to ablate bone and cartilage in vitro.[7] In addition, the capability to use optical fibers with this pulsed laser enhances the ability to deliver the beam to remote areas within the tracheobronchial tree and the larynx.

The hazard of endotracheal tube fire during laser laryngeal procedures is well known. Protective measures to avoid such complications include protective wrapping of endotracheal tubes, the use of specially designed laser tubes, and the use of apneic techniques, which avoid the use of a tube while the

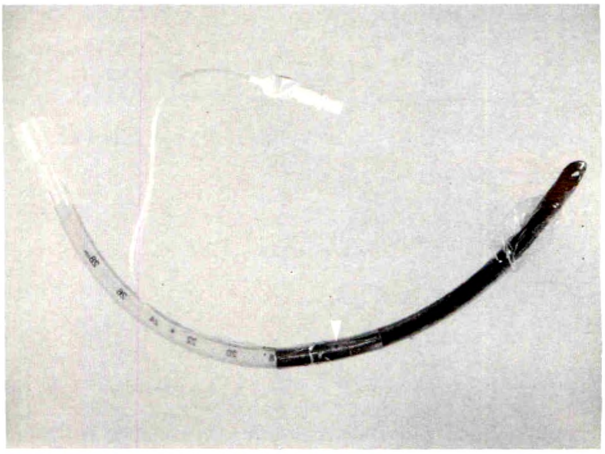

Fig 1. Endotracheal tube with aluminum foil tape impacted with 15 pulses of 1 J per pulse during use of erbium:yttrium aluminum garnet laser. Note charring of tube distal to impact site. Arrowhead — impact site.

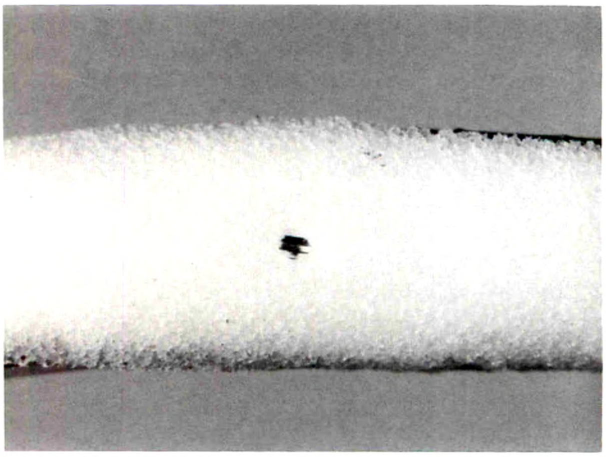

Fig 2. Merocel silver foil tape impacted with 600 pulses of 1 J per pulse during use of erbium:yttrium aluminum garnet laser. Note vaporization of Merocel sponge; however, silver tape is intact.

laser is operational. Aluminum tape wrapping has been shown to be effective in preventing endotracheal tube ignition with the CO_2 laser. Sosis[8] has pointed out, however, that the type of aluminum tape is critical. In a study comparing five metallic tapes, he observed that 3M tape number 425 was unaffected by a 25-second exposure of 70 W with the CO_2 laser in a continuous mode, while other aluminum tapes were perforated at lesser energy exposures. In our study, Mystic brand aluminum tape was used and was unaffected by a 240-second exposure to 20 W of CO_2 laser energy in the continuous mode.

Our study indicates that use of aluminum wrapping, commonly used with the CO_2 laser, would be inadequate to prevent endotracheal tube ignition during use of the Er:YAG laser. Corrugated silver tape, however, withstood 600 J of energy without evidence of injury. These findings can be understood by considering the absorption differences between silver and aluminum. The Hagen-Rubens relation (relating the infrared absorption to DC conductivity) indicates that both aluminum and silver have less than 2% absorption at 10 µm. At 3 µm, however, the silver tape absorbs approximately 1.5%, versus nearly 6% for the aluminum tape.

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EFFECT OF HELIUM CONCENTRATION ON EXPERIMENTAL UPPER AIRWAY OBSTRUCTION

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This study investigates the effect of helium concentration in inspired gas on resistance to breathing during experimental upper airway obstruction. Obstruction was modeled by use of a series of four polyvinyl endotracheal tubes narrowed progressively in their midportions with C clamps. Percentage ratios of helium-oxygen gas mixtures were 0:100, 40:60, 60:40, and 80:20. Gas flow was provided by two methods: 1) nontidal flow from compressed gas tanks from which resistance was calculated from pressure and flow measurements, and 2) tidal respiratory flow from human volunteers from whom respiratory effort was evaluated by using airway pressure measurements integrated over 90-second trial periods. The results derived from both methods demonstrated that the effect of helium in reducing resistance and pressure in an obstructed airway is linear ($p < .016$) and inversely proportional to helium concentration. Reductions in resistance and pressure were larger for the tighter obstructions ($p < .007$). As helium was added to the gas mixture (from 0% to 80%), resistance and airway pressure measurements dropped 42% and 58%, respectively. The major conclusions are that 1) even low concentrations of helium may have therapeutic value and 2) helium is effective only for more severe obstructions.

KEY WORDS — airway obstruction, helium.

INTRODUCTION

Although helium has been used clinically for over 50 years to improve pathologic obstruction in the upper airway,[1-6] its acceptance has not been widespread. Theoretically, helium-oxygen mixtures should be useful pharmacologic tools for the treatment of acute upper airway obstruction. Helium has a lower density by one tenth than nitrogen and oxygen and decreases the probability of turbulent airflow through stenosed airways. Reduction of turbulence decreases airway resistance.[7-9]

A major reason why the use of helium-oxygen is not more prevalent is the assumption that helium concentrations of less than 80% are clinically ineffective in relieving the turbulent flow resistance associated with upper airway obstruction. The mixture is most effective at its maximum concentration (helium 80%, oxygen 20%) and is usually given at maximum concentration when the patient has normal room air arterial oxygen saturation. Many patients with large-airway obstruction, however, have arterial oxygen desaturation due to hypoventilation, atelectasis, and concomitant lung disease; they require an augmented fraction of inspired oxygen (FiO2) to avoid hypoxia. As FiO2 is increased, helium becomes a smaller fraction of the inspired gas mixture and becomes less effective. Good experimental evidence to document the decrease in therapeutic effectiveness when lesser helium concentrations are used is lacking.[4,10]

This experiment was designed to study the effect of helium concentration on airway resistance due to upper airway obstruction and the impact of that effect on breathing effort.

MATERIAL AND METHODS

The gas mixture was a blend of medical-grade helium 80% and oxygen 20% with oxygen USP 99.5% (Liquid Carbonic Corp). The gases were mixed with a Bird High Flow Oxygen Blender (3M Co, St Paul, Minn). Flow was controlled by an oxygen flow meter (Precision Medical, 1MFA1001, Bath, Pa) previously calibrated for helium-oxygen mixtures. Oxygen concentration was measured by an Ohio Oxygen Monitor 401 (Airco, Inc, Madison, Wis) (Fig 1A,B).

Upper airway obstruction was modeled by use of a series of 10-mm (inner diameter) endotracheal tubes cut into 6- to 7-cm lengths. Fixed, fusiform obstructions of various degrees were obtained by use of a screw-type tubing clamp (Fig 2). The highest degree of obstruction (D) was established subjectively as the average largest resistance tolerated by the three investigators while breathing room air by mouth for 90 seconds. The least obstruction (A) was set at a level that represented the average smallest resistance that could be sensed. The other two obstructions (B and C) were set at levels between those of A and D.

Part 1: Nontidal Flow. The resistance of flow for each artificial obstruction was determined for vari-

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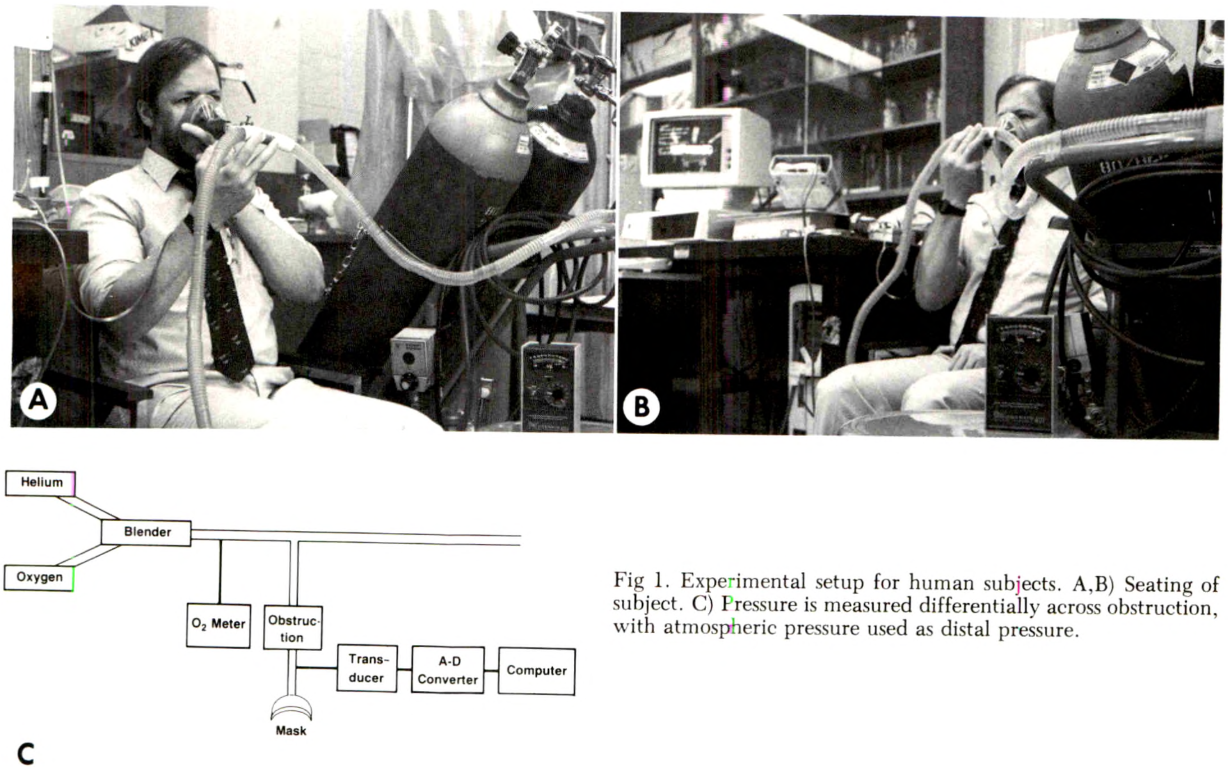

Fig 1. Experimental setup for human subjects. A,B) Seating of subject. C) Pressure is measured differentially across obstruction, with atmospheric pressure used as distal pressure.

ous concentrations of helium during constant unidirectional flow (Fig 3). Pressure was measured differentially across each obstruction by use of a water manometer. Flow was measured by a rotameter (F1500, Gilmont Instruments, Inc, Great Neck, NY), previously calibrated at atmospheric pressure for each gas mixture. Obstructions A, B, C, and D were tested at five flow rates and four helium-oxygen ratios (0:100, 40:60, 60:40, and 80:20).

Resistance to flow for each helium concentration was derived by measuring the pressure at various flow rates, both within and above the physiologic range.[11] Resistance to flow can be calculated as $R = P/F$ where R is resistance (cm H_2O per L/min), P is differential pressure across each obstruction (cm H_2O), and F is flow (L/min).

Linear regression analysis (Minitab) was used to calculate the slope of the relatively linear part of the pressure-flow curves. The slope (P/F) was used as an estimate of the resistance (R). See Results for further discussion.

Part 2: Human Subjects. Approval for human experimentation was obtained from the Clinical Investigation Committee at The Milton S. Hershey Medical Center. The subjects were five healthy, nonsmoking men between the ages of 23 and 35. Informed consent was obtained individually.

The blended gases were passed through flexible tubing to the subjects. Oxygen concentration was monitored adjacent to the blender, at a point at which variations from tidal respiration were minimized (Fig 1C). A T-piece adaptor was inserted into the flexible tubing to attach the artificial obstruction and/or the face mask. One and one-fourth meters of reservoir tubing was extended beyond the T-piece to minimize contamination by room air during inhalation. All trials were performed at a total fresh gas flow rate of 10 L/min, which was greater than any subject's respiratory minute volume, as determined in preliminary studies with a pneumotachometer. The artificial obstructions and gas mixtures were the same as in part 1.

Data collection periods of 90 seconds were begun after pressure tracings for inhalation and exhalation had stabilized. Each subject sat erect and held the mask tightly to his face to minimize leaks. Twenty trials were conducted for each subject at each of the five obstructions (none, A, B, C, D) and each of the four gas mixtures, starting with 100% oxygen.

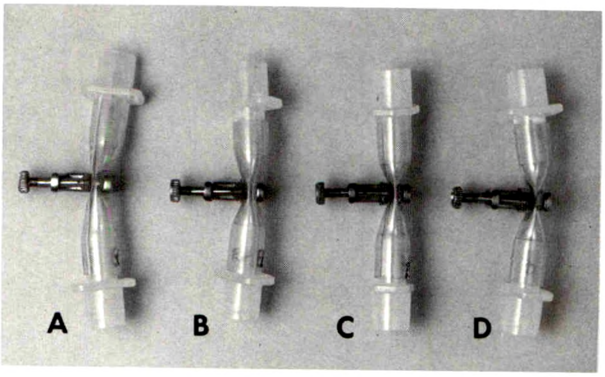

Fig 2. Artificial airway obstructions. A is mildest; D is tightest.

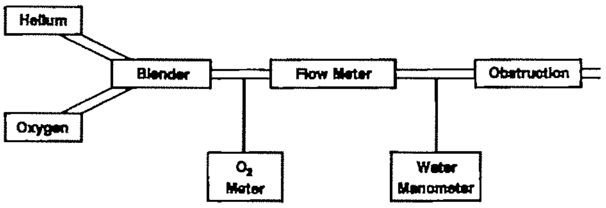

Fig 3. Experimental setup for continuous unidirectional flow.

The pressure gradient across each obstruction was measured with a differential pressure transducer (MP45-30, ±80 cm H_2O; a linear response over the range of testing was confirmed by a water manometer) with a carrier demodulator (CD-18, Validyne Engineering Corp, Northridge, Calif). The pressure proximal to the obstruction was compared to atmospheric pressure. The transducer was calibrated with a water manometer before each study.

All data were digitally collected and analyzed. Analog-to-digital conversion was performed by an ISAAC 2000 data acquisition system (Cyborg Corp, Newton, Mass) with 12-bit precision at a sample rate of 50 Hz. Data storage and analysis were performed on an IBM PC-XT microcomputer with programs written by one of the investigators.

The pressure-time integral (PTI)[12-14] of the inspiratory phase of respiration was measured as an indicator of muscular respiratory effort (Fig 4). The inspiratory phase was used because the inspiratory PTI is an excellent marker of respiratory muscular effort (see Discussion) and because mask leaks are minimized during inspiration.

Statistical studies suitable for repeat-measures ANOVA were performed with BMDP statistical software (PV2) and a BMDP statistical analysis system (SAS, GLM procedure). A p value of $<.05$ was considered to be statistically significant.

RESULTS

Nontidal Flow of Compressed Gas. The results for the 80% helium–20% oxygen mixture are presented in Fig 5A as an example of the flow-pressure measurements taken for each gas mixture. Flow-pressure measurements for the other gas mixtures are not shown; however, the calculated resistance values for each of the mixtures are summarized in Fig 5B. The pressure needed to maintain a specific flow rate increases as the tightness of the obstruction increases (A through D).

The curves in Fig 5A are not linear, making the calculation of a single resistance value impossible. However, flow-volume studies have demonstrated the peak inspiratory flow rate for quiet respiration to be, at most, 30 L/min; the average inspiratory flow rate is 5 to 6 L/min.[11] For flows in the physiologic range (<30 L/min; Fig 5A), the curves are nearly linear. For these lower flow rates, the resistance for each artificial obstruction can be estimated as the slope of the lower part of each curve. The slopes were calculated by linear regression with the results from the three lowest flow rates. The R^2 values, adjusted for 2 *df*, were between 91.9% and 97.3%. Although these high R^2 values do not prove linearity, since only three points are involved, they do indicate that linearity is a good approximation. A summary of airway resistances as a function of helium concentration is presented in Fig 5B and includes all gas mixtures tested.

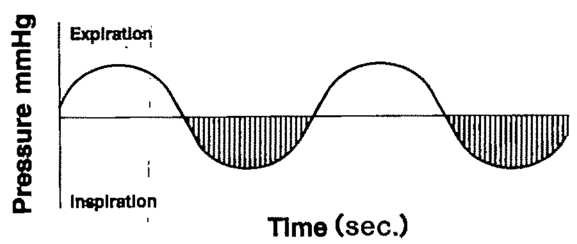

Fig 4. Calculation of pressure-time integral.

The decrease in resistance from 0% helium to 80% helium is 41%, 45%, 41%, and 40% for obstructions A, B, C, and D, respectively, with a mean of 42%.

Tidal Flow in Human Subjects. The relationship between the PTI and the helium concentration is presented in Fig 5C. The mean values of the PTI for the five subjects are shown. The PTI varies continuously over the range of helium concentrations, and the relationship is linear, being inversely proportional to the helium concentration. Using the ANOVA test for linear trend, the relationship is indeed linear, with $p<.0156$.

The decrease in the PTI from 0% helium to 80% helium is 64%, 69%, 54%, and 47% for obstructions A, B, C, and D, respectively, with a mean of 58%.

The range of PTI values varies considerably from subject to subject (Fig 6). For example, values for breathing 100% oxygen through the tightest obstruction (D) range from a low of 498 to a high of 964.

DISCUSSION

These data demonstrate that helium-oxygen mixtures decrease both resistance to flow and breathing effort for severe obstruction when helium concentrations are less than 80%. The effect of helium concentration in the inspired gases in reducing resistance and effort is linear across a range of concentrations from 0% to 80%. No plateau or threshold is seen.

For nontidal flow (Fig 5B), the slope of the line for the mildest obstruction (A) is nearly zero; there

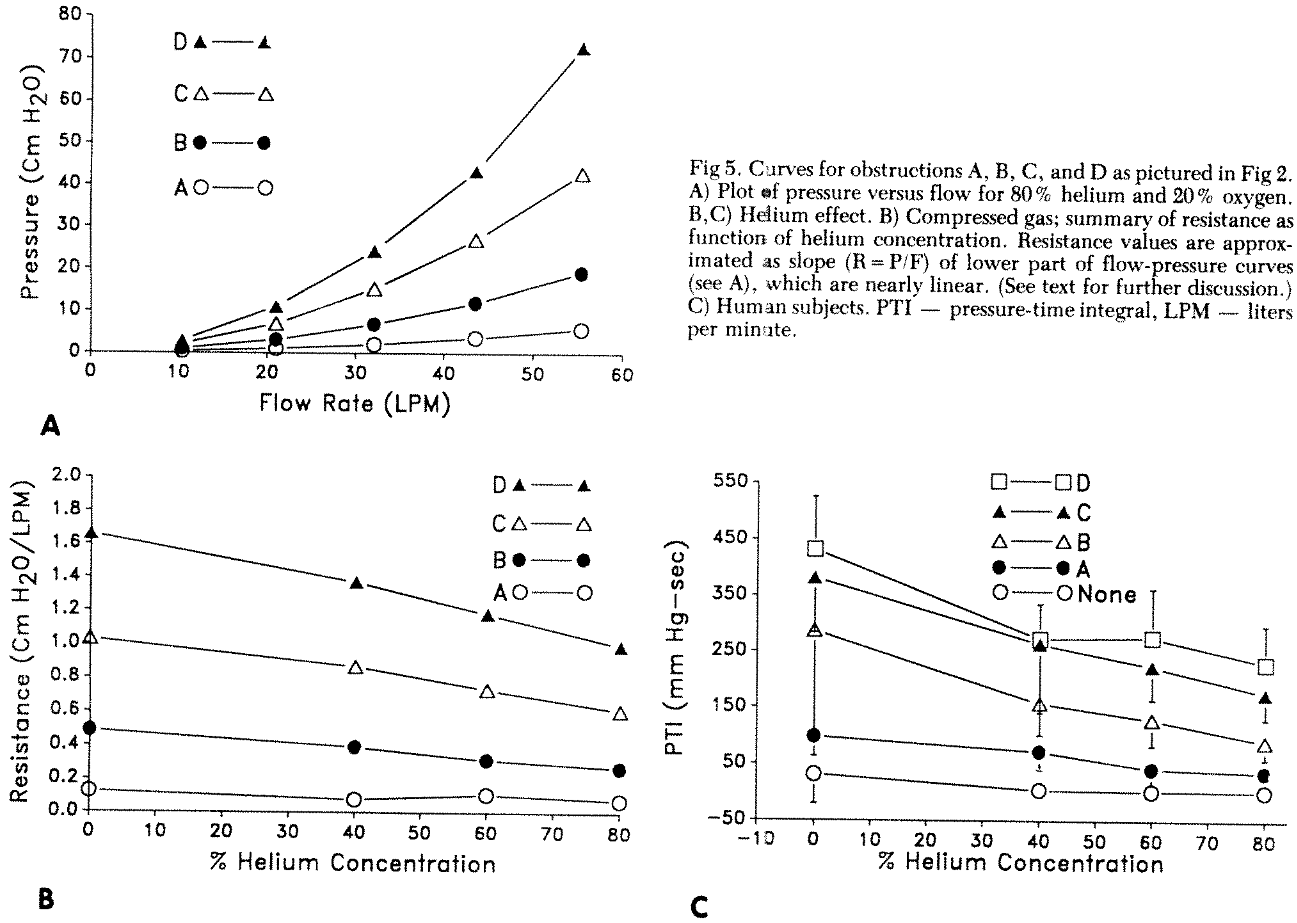

Fig 5. Curves for obstructions A, B, C, and D as pictured in Fig 2. A) Plot of pressure versus flow for 80% helium and 20% oxygen. B,C) Helium effect. B) Compressed gas; summary of resistance as function of helium concentration. Resistance values are approximated as slope (R = P/F) of lower part of flow-pressure curves (see A), which are nearly linear. (See text for further discussion.) C) Human subjects. PTI — pressure-time integral, LPM — liters per minute.

is no significant change in resistance as helium concentration is changed. Most likely, obstruction A produced little or no turbulence; thus, helium had little effect. The effect of helium becomes more apparent as the obstruction becomes tighter and, presumably, more turbulence is produced. For each obstruction, the relationship between resistance and helium concentration is linear.

For tidal flow (Fig 5C), the helium effect is very small when there is no or very mild obstruction (A); the slope of these lines is not significantly different from zero. However, the effect is significant for the tighter obstructions (B, C, D), with $p < .0001$ for *t* tests on the slope coefficients. As an example, with the tightest obstruction (D), the PTI dropped from 432 to 229, a decrease of 47%. Generally, the tighter the obstruction, the greater the effect of helium ($p < .007$ for the F test), probably because of increased turbulence with the tighter obstructions. However, the difference between the slopes of the curves of obstructions C and D was very small. Obstruction D was quite tight, at the limit of tolerance for the subjects, and obtaining reliable results was difficult because of the considerable effort necessary to sustain respiration.

The same result was obtained whether flow rate was nontidal (compressed gases) or tidal (human subjects). Because airway resistance is dependent on gas flow or velocity (see equations 1 and 2, below), we were uncertain that the effect of helium concentration would be similar with either nontidal flow rates from compressed gas or varying flow rates from tidal breathing. If such a difference exists, it was not detected in this experimental setting.

The model obstruction was chosen to be fusiform and slitlike, rather than a narrow tube or an orifice, to more resemble the shape of obstructions seen clinically. In a patient, an acutely obstructed airway is probably more irregular than our model obstruction and is more likely to produce turbulence. Thus, our obstruction model tends to underestimate the effect of helium in comparison to real-life situations.

The linear relationship between helium concentration and resistance to flow is predictable on the basis of fluid mechanics. Helium has two major effects in reducing resistance in an obstructed airway. First, helium reduces the probability of turbulence. Flow of air in the upper airway is turbulent, except at rest, because of the rough walls of the airway and the relatively short lengths of the airway segments compared to their diameters.[7,15] The probability of turbulent flow is predicted in equation 1 by the Reynold's number (dimensionless):

$$N_R = \frac{V \cdot D \cdot d}{n} \quad (1)$$

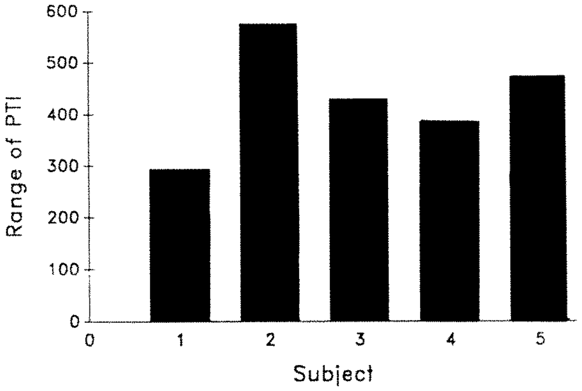

Fig 6. Range of pressure-time integral (PTI) values for human subjects.

in which V is gas velocity (cm/s), D is tube diameter (cm), n is gas velocity (poise), and d is gas density (g/cm^3). In a smooth-walled tube, if N_R is above 3,000, the probability of turbulent flow is very high; if it is below 2,000, the probability is quite low. However, if the tube has rough walls, as the trachea would, turbulence may appear at flow rates lower than predicted. The lower density of a gas such as helium results in a lower probability of turbulent flow. Less turbulence results in lower resistance to flow.[15] Density is a linear (first-degree) factor in the equation.

Second, as in equation 2, gas flow through an orifice requires an increase in pressure to maintain the flow:

$$P = \frac{d}{2C^2}\left(\frac{1}{A2^2} - \frac{1}{A1^2}\right)F^2 \tag{2}$$

where P is the pressure difference caused by the orifice (dynes/cm^2), A1 and A2 are the areas of the tube and orifice (in cm^2), F is flow (cm^3/s), and C is the discharge coefficient, which depends on the sharpness of the edge of the orifice. Again, density is a linear factor.

Since gas density is a first-degree factor in equation 2, the resistance of an obstructed airway should vary linearly with gas density. Therefore, results from both experimental settings (constant flow and tidal flow) were predicted qualitatively by these equations.[7,16]

Variations of helium concentration had little effect on airway resistance when low-grade obstructions were used (obstructions A and B). Most likely, mild obstruction produced little turbulence in the flow of air.

Variation in helium concentration had a significant effect when obstruction was increased (obstructions C and D). Yet helium did not reduce resistance to the levels seen with no obstruction (Fig 5B,C). Although the trials were not performed with 100% helium, the effect is linear over the range of 0% to 80% and probably extends to higher concentrations. The resistance did not fall to nonobstructed levels, because although helium decreases the amount of turbulence in a flow system, it cannot eliminate turbulence entirely.

The PTI was used as the experimental parameter for part 2 (human subjects) for several reasons. First, the major portion of energy expended by active skeletal muscle is caused by force generation (tension) and its duration (time). The resultant sum of the tensions generated by inspiratory muscle activity is the pressure that drives respiratory gas flow[12]; in a stenosed airway, the major portion of this generated pressure is expended in forcing gas through the area of obstruction. It is this inspiratory pressure, integrated over time ($\int Pdt$), that was measured as the PTI.

Second, the inspiratory PTI is an excellent marker of respiratory muscular effort, and a high PTI is a reliable predictor of hypoventilatory respiratory failure.[17] Human studies have shown a high correlation between the diaphragm PTI and oxygen consumption attributable to respiratory muscle metabolism.[13] In addition, a high diaphragm tension time index (an indexed PTI) is associated with diaphragm fatigue.[14]

Although we believe that the time integral of the obstructive pressure drop during inspiration is an accurate correlate of the overall respiratory muscle effort, there are three ways in which the PTI, when measured across the obstructive model, may underestimate the total respiratory muscle effort. First, the hyperinflation induced by increased airway resistance is likely to diminish the compliance of the respiratory system and thereby induce an increase in the elastic work of inspiration, which will not be reflected in the PTI.[18] Second, the increase in lung volume is likely to cause a decrease in respiratory muscle efficiency as the diaphragm acquires a flattened radius of curvature and loses its optimal curved shape.[19] Finally, this model does not assess expiratory muscle effort. In contrast to normal tidal breathing, which is powered by the elastic recoil of the thoracic wall and lungs, expiration against a fixed resistance may be additionally powered by abdominal muscle contraction; such efforts would not be measured by the system that we have employed. However, there is no evidence to suggest that such expiratory effort contributes to respiratory muscle fatigue or respiratory failure.

By this reasoning, it is possible that the PTI, as we have measured it, underestimates the true muscular effort associated with breathing through an increased resistance. To the extent that this is true, the PTI is likely, as well, to underestimate the therapeutic impact of a given helium concentration on respiratory muscle loading.

The subjects demonstrated a wide variation in the range of values for the PTI that suggested individual differences in response to external loading (Fig 6). Especially with the severe obstructions, anxiety and discomfort may have contributed to higher airway pressures and therefore a higher PTI. Part of the explanation for the dramatic decreases in the PTI seen with breathing helium-enriched mixtures may be the role of obstruction-induced agitation that provoked less than optimal (high flow rate) respiratory efforts; this was especially noted when the obstruction was the greatest (D; Fig 5C). If a decrease in perceived resistance to airflow results in reduced anxiety, a less energy-consuming respiratory pattern might follow, thereby diminishing the likelihood of exertion-induced muscle fatigue.

Several conclusions and clinical implications can be drawn from this study. The relationship between helium concentration and the effect of helium on airway resistance is linear; no sudden drop-off or plateau exists. Thus, even low concentrations of helium may be beneficial in an acute clinical situation. In the hypoxic patient with severe airway obstruction, PO2 may be improved in two ways. The addition of helium may somewhat improve PO2 by improving ventilation and decreasing the shunt. More important, increases in FiO2 directly increase the gradient for O2 transfer at the alveolar-capillary interfaces. The relative contributions of helium and elevation of FiO2 to the improvement of hypoxia are difficult to predict and may depend upon the anxiety and the breathing pattern of the patient. The oxygen saturation of the patient should be monitored closely, preferably with ear or pulse oximetry, and the concentrations of oxygen and helium adjusted accordingly. The FiO2 should be only high enough to maintain adequate oxygen saturation of the blood, and the maximum concentration of helium that is compatible with adequate oxygen saturation should be used.

With mild degrees of obstruction, little turbulence is expected. Helium does not decrease resistance in these situations and would not be expected to be helpful to a patient having little respiratory distress.

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MALIGNANT TRANSFORMATION IN A LARYNGEAL HEMANGIOMA

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Laryngeal angiosarcoma is uncommon, with only 19 previously reported cases. Malignant transformation in nonirradiated hemangiomas is extremely rare, with only five equivocal cases reported, all of which occurred in the skin. We report the first documented case of malignant transformation in a laryngeal hemangioma, and review the literature.

KEY WORDS — angiosarcoma, larynx.

INTRODUCTION

Angiosarcoma usually arises in viscera and bones,[1] but also is described in the skin as a complication of long-standing lymphedema of the extremities and following radiotherapy. There have been 19 previously reported cases of laryngeal angiosarcoma.[2-5] None of these cases, however, had histologic confirmation by immunochemical demonstration of endothelium by means of endothelial markers such as factor VIII–related antigen or *Ulex europaeus* lectin. Batsakis and Fox[6] doubted the accuracy of the histologic diagnosis in many instances of the 15 cases of laryngeal angiosarcoma described by Pratt and Goodof.[2] We report the first documented case of laryngeal angiosarcoma arising in a preexisting benign hemangioma, and review the literature.

CASE REPORT

A 24-year-old woman presented to her local hospital with acute dyspnea following an 18-month history of discomfort in the throat and intermittent hemoptysis. With general anesthesia, a tracheostomy was performed and a pedunculated right subglottic swelling removed endoscopically, histologic examination of which showed blood clot and exudate only.

Postoperatively, bleeding continued and the larynx was explored through a laryngofissure. A biopsy was done of a right subglottic ulcer, histologic examination of which yielded results consistent with a diagnosis of benign hemangioma.

Bleeding continued over the next 18 months, and she was referred to St Bartholomew's Hospital, where a right subglottic vascular mass was removed at laryngofissure, histologic examination of which again yielded results consistent with a diagnosis of hemangioma (Fig 1A).

Intermittent bleeding, however, continued; over the next 22 months biopsies on three separate occasions and a further laryngofissure with macroscopic clearance of the subglottic tumor again failed to demonstrate malignancy.

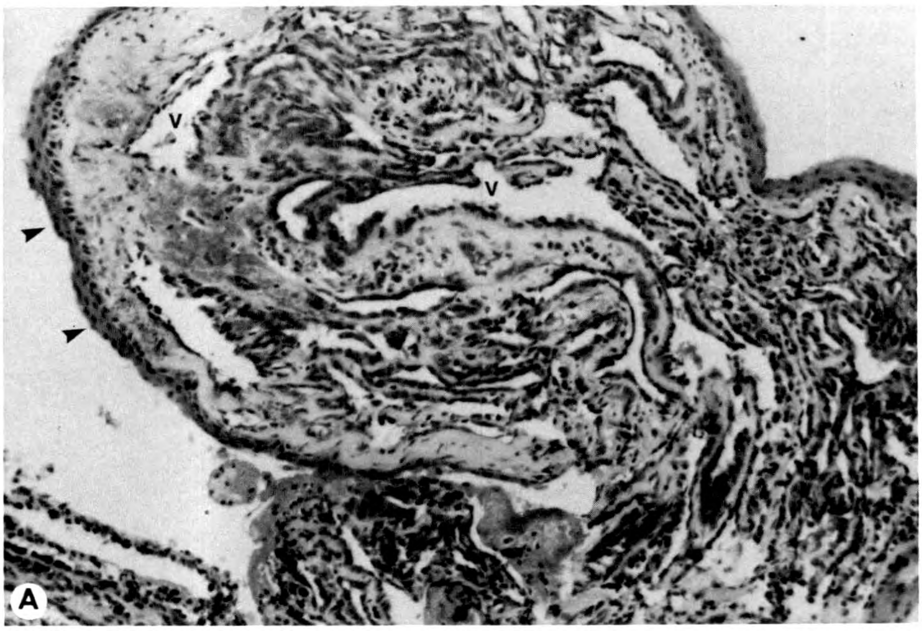

Fig 1. Histologic specimens. A) First biopsy specimen (H & E, original x180). Polypoid tumor covered by squamous epithelium (arrowheads) and composed of well-formed vascular channels (v) lined by plump endothelium with minimal nuclear pleomorphism and no mitotic activity. Appearances are those of benign hemangioma. (Continued on next page.)

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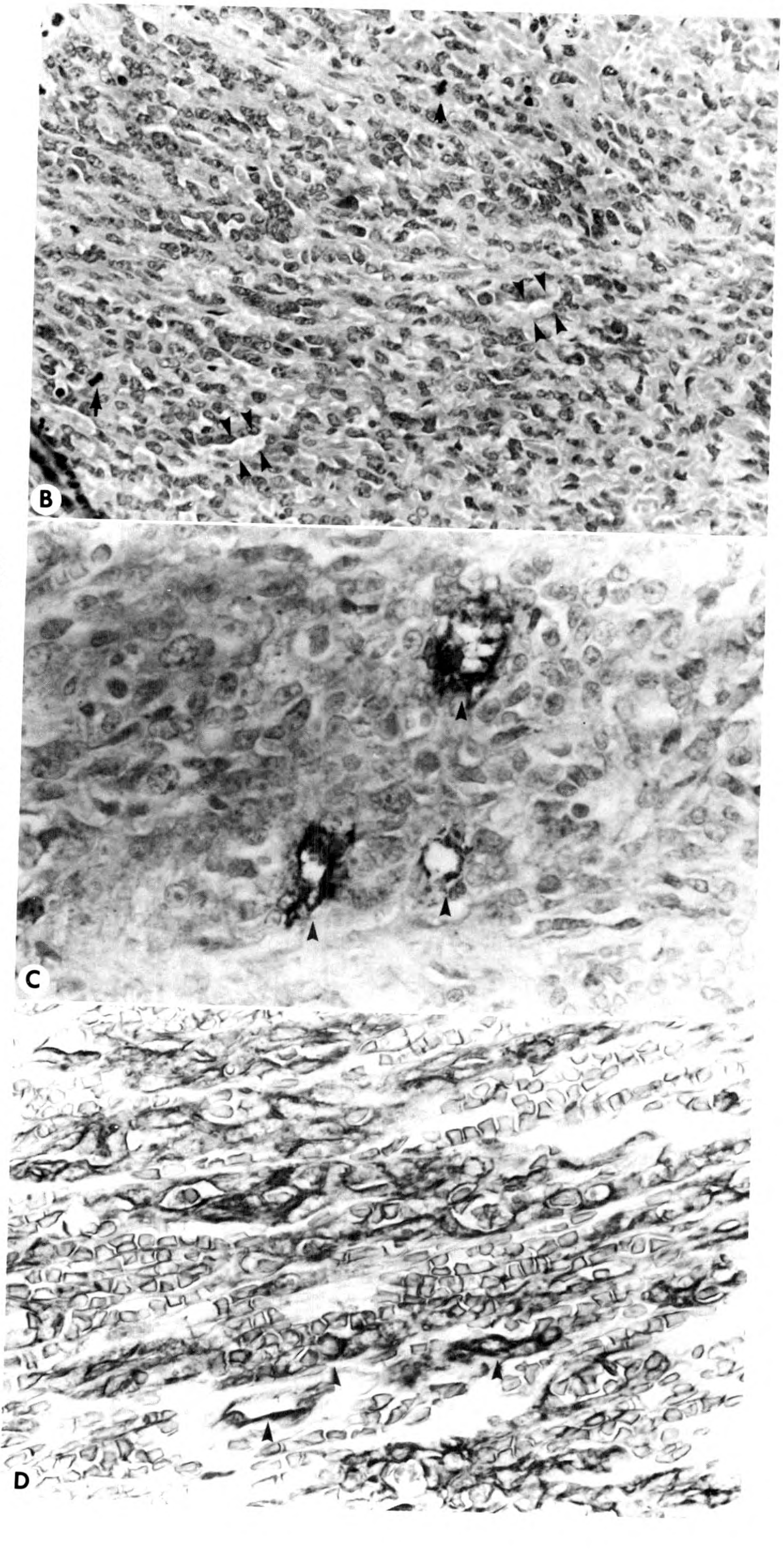

Fig 1, continued. B) Biopsy specimen (H & E, original x450). Solid sheets of pleomorphic tumor cells are seen, with increased mitotic activity (arrows) and slitlike spaces (arrowheads) containing red cells. Features are those of poorly differentiated angiosarcoma. C,D) Laryngectomy specimens. C) Undifferentiated sheets of tumor cells with occasional vascular lumena showing cytoplasmic and luminal granular positivity for factor VIII–related antigen (arrowheads) (diaminobenzidine immunoperoxidase, original x480). D) Another portion of tumor, composed of irregular slitlike vascular spaces showing patchy granular positivity for *Ulex europaeus* lectin (arrowheads) (biotinylated *U europaeus* with avidin-biotin-peroxidase complex, original x480).

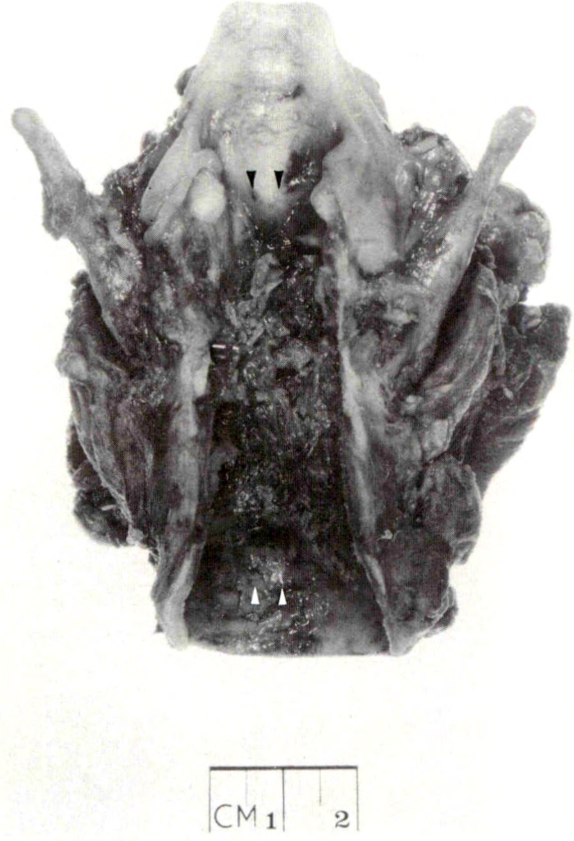

Fig 2. Operative specimen. Larynx has been opened posteriorly to reveal hemorrhagic nodular and ulcerated tumor (between arrowheads) obliterating vocal cords and extending close to lower resection margins.

Four months later, laryngeal stenosis was noted and dilated endoscopically; biopsy at this time showed no evidence of malignancy. Subsequent removal of the laryngeal stent revealed an apparently healing subglottis.

Six months later, over 5 years after the first onset of symptoms, she developed a mass in the neck, biopsy of which showed hemangiosarcoma (Fig 1B). Laryngoscopy at this time showed extensive invasion of the larynx by the tumor.

Computed tomographic scanning of the neck and chest and bone and liver scintiscans with technetium 99m suggested tumor confined to the neck, and total laryngectomy was carried out with excision of the anterior neck skin (Fig 2) and deltopectoral flap reconstruction. Histologic confirmation of the diagnosis was obtained by immunochemical staining using factor VIII–related antigen (Fig 1C) and *Ulex europaeus* lectin (Fig 1D).

Tumor was found at the margins of the resection, however, and recurrence in the neck rapidly occurred despite external beam radiotherapy and systemic cytotoxic chemotherapy. She developed widespread metastatic disease and died 10 months after the laryngectomy.

DISCUSSION

The incidence of sarcomatous laryngeal tumors is less than 1% of malignant laryngeal tumors.[4,5,7,8] There are three clinicopathologic variants of malignant vascular tumors, comprising angiosarcoma, hemangiopericytoma, and Kaposi's sarcoma. Historically, lymphangiosarcoma was described separately from angiosarcoma in association with edematous extremities secondary to radical mastectomy[9] or vascular stasis.[5] Lymphangiosarcoma, however, is histologically identical to angiosarcoma.[1,10-13] Maddox and Evans[13] showed that these angiosarcomas, those of the scalp and face, and those arising after radiotherapy are manifestations of a single tumor entity. This they called cutaneous-subcutaneous angiosarcoma. Cutaneous-subcutaneous angiosarcoma has been described in association with previous radiotherapy in both the presence[12,14,15] and absence[16-18] of preexisting hemangioma.

There have been five previously reported cases of sarcomatous change in patients with unirradiated preexisting hemangioma. Girard et al[12] described low-grade angiosarcoma arising in port-wine stains on the backs of three children; Wilson Jones,[19] however, doubted this diagnosis and suggested that these lesions can be allocated to special categories including pyogenic granuloma with recurrent satellites and hemangioma with capillary tufts. Two cases have been described of Maffucci's syndrome, in which multiple enchondromas and cutaneous hemangiomas coexist; Bean[20] described one case of metastatic angiosarcoma, but this patient had no documented hemangiosarcoma at the site of a previous hemangioma and had received radiotherapy. Davidson et al[21] described one patient with suprapatellar hemangiosarcoma, but there was no evidence of cutaneous hemangioma at this site.

Thus, review of the world literature reveals that the present case is the first unequivocal documented case of sarcomatous transformation in a hemangioma occurring in normal unirradiated tissue.

Hemangiosarcoma is characteristically a highly malignant tumor[3,4]; Maddox and Evans[13] reported a mean survival of 20 months. Our patient lived 10 months after diagnosis, having been in good health for the preceding 4 years, despite the subglottic hemangioma.

These tumors have a poor prognosis,[10-12,22,23] and surgical excision combined with wide field irradiation is the treatment of choice.[23,24] A feature of our case was the resistance of the tumor to radiotherapy. These tumors are recognized to be of variable radiosensitivity: some authors report good palliation,[19,22] while others report complete radioresistance.[10,12]

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QUANTIFICATION OF THE RELATION BETWEEN ELECTROPHYSIOLOGIC AND MORPHOLOGIC CHANGES IN EXPERIMENTAL ENDOLYMPHATIC HYDROPS

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The degree of hydrops in guinea pig ears that had undergone unilateral endolymphatic sac and duct obliteration was quantified. For 15 guinea pigs from a prior study, the correlation between the degree of hydrops and several electrophysiologic measures of the functional state of the cochlea was determined. A significant correlation between the degree of hydrops and a reduction in the low-frequency cochlear microphonic evoked by a 29-Hz tone was found. No correlation was found between the degree of hydrops and the magnitude of the summating potential evoked by 8-kHz probes. A weak correlation was found between the degree of hydrops and a reduction in the compound action potential evoked by 2-kHz probes. Possible differences in the way the endolymphatic duct obliteration exerts its effect on the different cochlear potentials are discussed.

KEY WORDS — electrocochleography, endolymphatic hydrops, histology.

INTRODUCTION

The most widely used experimental approach toward obtaining a better understanding of Meniere's disease is the inducement of endolymphatic hydrops in the inner ears of animals.[1] The technique of inducing an endolymphatic hydrops by obliteration of the endolymphatic duct and sac was developed by Kimura and Schuknecht[2] and later modified by Konishi and Shea.[3]

The most conspicuous morphologic changes in the first 3 months after obliteration are distension of Reissner's membrane, degeneration and loss of outer hair cells, and degeneration of the stria vascularis.[4-6] Longer postoperative periods show a complete degeneration of the organ of Corti, which is much more severe than the degeneration that is generally found in the organ of Corti of Meniere's patients.

Electrophysiologic changes after short postoperative periods may include an increase of the summating potential when measured at the apex[7]; fluctuating thresholds of the compound action potential (AP) evoked by low-frequency tone bursts[8]; and a decrease in the low-frequency cochlear microphonic (LFCM).[9,10]

Common to all electrophysiologic and morphologic changes is the large variability among animals. We therefore performed a quantitative analysis of the relation between morphologic and electrophysiologic changes in early endolymphatic hydrops. Measurements of the degree of hydrops in an animal were compared with electrophysiologically acquired data. In this way, we hoped to gain more insight into the development of the effects and their interrelations. The electrophysiologic results analyzed in this paper have been published before as averages over groups of ears.[9]

MATERIALS AND METHODS

Seventeen healthy, albino guinea pigs were used in this experiment. Animal surgery and electrophysiologic data acquisition have been described before[9] and will not be discussed here. The right ear of each animal was operated on. The left one was used as a control. There were no conspicuous changes in the left ears, compared to ears of nonoperated animals, neither morphologically nor electrophysiologically. After 2 weeks (nine animals) or 4 weeks (eight animals), electrophysiologic measurements were performed on both ears of each animal. The electrode was placed near the round window. Potentials pertinent to this paper were the LFCM evoked by a 29-Hz tone; the summating potential (SP) evoked by 8-kHz probes; and the AP evoked by 2-kHz probes. These frequencies were chosen from the ones available[9] because at these frequencies the effects of the operation were relatively clear, when averages across ears were compared.

After the electrophysiologic experiment, fixation was performed transcardially with a trialdehyde fixative (3% glutaraldehyde, 2% formaldehyde, 1% acrolein, and 2.5% dimethylsulfoxide in 0.08 mol/L sodium cacodylate buffer; pH 7.4). The temporal bones were removed and decalcified in 10% sodium EDTA (pH 7.4). After about 2 weeks, they were postfixed in 1% osmium tetroxide and dehydrated in a graded ethanol series. They were em-

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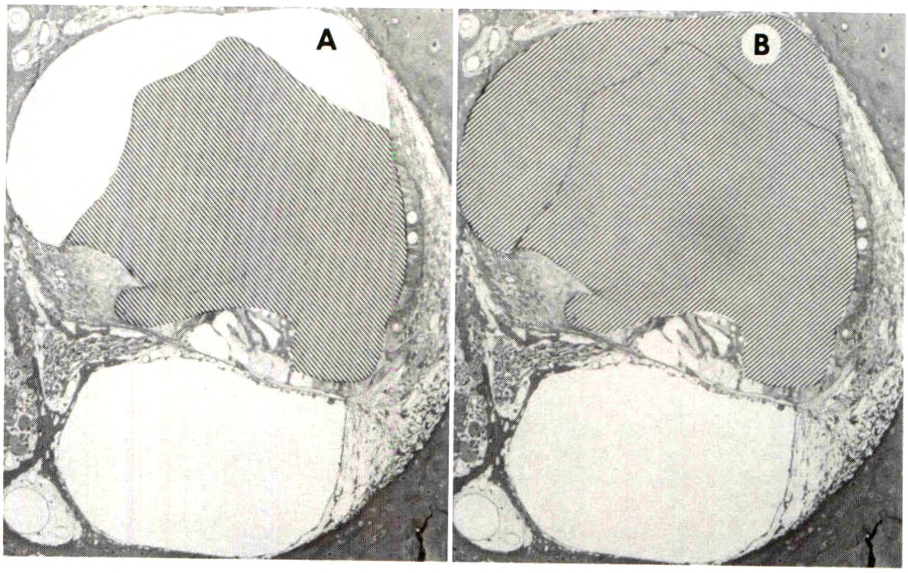

Fig 1. Measurement of proportional area. A) Area of scala media (hatched region). B) Area of scala media and scala vestibuli (hatched region).

bedded in Spurr's low-viscosity resin. Subsequently, the cochleas were divided into two parts along the midmodiolar plane and reembedded in Spurr's low-viscosity resin. Semithin sectioning (1 μm) as close as possible and parallel to the midmodiolar plane was performed. The sections were stained with methylene blue and azure B.

The sections were projected on the video screen of a Quantimet 720 Image Analyzer for quantitative analysis. The area of scala media (SM) and scala vestibuli (SV) was measured in each turn of the cochlea on both the right side and the left side of the modiolus. This procedure was performed for both ears, the operated right ear and the nonoperated left ear, of each animal. The procedure was performed on two sections per ear. Thus, we had four measurements per turn, and the average of these measurements was calculated. In order to compensate for deviations in the plane of sectioning, the ratio of SM area to SM + SV area was calculated for each turn in both ears of each animal (Fig 1). This was called the proportional area. For each turn, we divided the proportional SM area from the right ear by the proportional SM area from the left ear. This ratio was called the SMA ratio. In formula:

$$\text{SMA ratio} = \frac{\left(\dfrac{\text{SM area}}{\text{SM area} + \text{SV area}}\right) \text{right}}{\left(\dfrac{\text{SM area}}{\text{SM area} + \text{SV area}}\right) \text{left}}$$

One of the reasons for using the ratio of right to left ear is that in order to correlate histologic data with electrophysiologic data it is necessary to have one data point for each of these features. Another reason is that using ratios compensates for inter-animal variability in anatomy. The ratio is close to 1 if there is no difference between the right and left ear; it is smaller than 1 if there is a collapse of Reissner's membrane; and it is larger than 1 if there is endolymphatic hydrops in the right ear. As a measure of the effect of the operation, the maximum of the SMA ratio was used, regardless of the turn in which it occurred. It should be emphasized that using the maximum SMA ratio is an arbitrary choice. Other procedures, for instance the one used by Shinkawa and Kimura,[11] might be equally valid for quantifying the hydrops, but cannot be used to correlate electrophysiologic and histologic data. We have tried some other procedures to calculate ratios, including ST area and the perimeter of all scalae. However, we have adopted the procedure above because of its simplicity and because the results were still compatible with more subjective ratings like mild, moderate, and severe. One might also propose to use the average of the SMA ratio over all turns instead of the maximum SMA ratio. However, the hydrops was frequently confined to one or two turns. Therefore, this alternative procedure would not discriminate very well.

Two animals were eliminated from the calculations because of poor histology of the left ear. Thus, we had a quantitative estimate of the effect of the operation on cochlear morphology for 15 animals in two postoperative groups.

The product-moment correlation coefficient was calculated for the relation between this morphologic measure and the electrophysiologic measures. For this purpose, the electrophysiologic data from the two ears of one animal had to be transformed into one measure. This was performed in several ways, described in the Results section. The validity of the procedure of using correlation coefficients was checked by use of the Kolmogorov-Smirnov test for normality on all morphologic and electrophysiologic data. The null hypothesis, that the data stem from a normal distribution, could be accepted for all cases ($p > .95$). The correlation coefficients were corrected for small sample size according to the method of Kendall and Stuart, described by Sokal and Rohlf.[12]

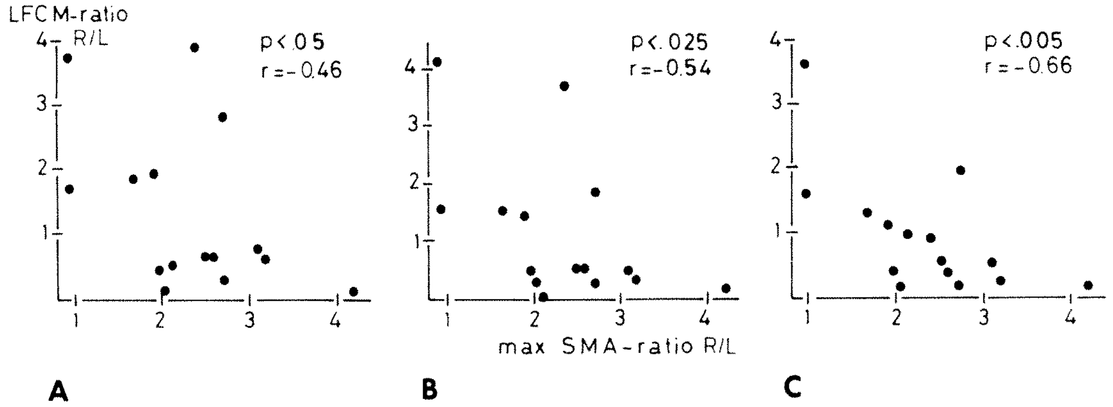

Fig 2. Scatterplots of ratio of low frequency cochlear microphonic (LFCM right/LFCM left) versus maximum scala media area (SMA) ratio for three levels of 29-Hz tone. Correlation coefficients are indicated in each plot together with their significance (p values). A) 94 dB sound pressure level (SPL). B) 84 dB SPL. C) 74 dB SPL.

RESULTS

The degree of hydrops reflected in the maximum SMA ratio found in the 2-week group did not differ significantly from the result in the 4-week group. In the 2-week group, the average maximum SMA ratio was 2.39 ± 0.96 (SD), while in the 4-week group it was 2.27 ± 0.76 (SD). On the basis of these findings, the data from the 2- and 4-week groups were pooled.

The LFCM in response to a 29-Hz tone was measured in all ears. When the LFCM from the right ears was compared with the LFCM from the left ears, analysis of variance revealed that the LFCM in the right ears was significantly smaller.[9] For each animal, the ratio of the LFCM in the right ear to the LFCM in the left ear was calculated. Scatterplots of this ratio for three levels of the 29-Hz tone against the maximum SMA ratio are presented in Fig 2. The LFCM ratio decreases with increasing maximum SMA ratio. The correlation coefficients are indicated in Fig 2; the correlation was significant at each of the three levels. The highest degree of correlation was found at the lowest level of the 29-Hz tone (Fig 2C), and the lowest at the highest level of the 29-Hz tone (Fig 2A).

Because the SP for 8 kHz at the round window was negative in some cases, we decided to use the difference between right and left ears as a measure for the effect of the hydrops. The difference of the SP between right and left ears in this group of animals was most marked for high-level, 8-kHz probe tones,[9] the SP being higher in the operated ear. This difference was not significant when averages across ears were compared in *t* tests. In Fig 3, scatterplots for the difference in the SP versus the maximum SMA ratio are presented for three levels of the 8-kHz probe tone. There is no significant correlation between the maximum SMA ratio and the difference in SP.

Klis and Smoorenburg[9] described smaller APs in the operated ear for 2-kHz, low-level probes. This difference was significant in *t* tests comparing the averages over right and left ears. We calculated the ratio of the AP from the left ear to the AP from the right for each animal. In Fig 4, scatterplots of this ratio versus the maximum SMA ratio are presented together with correlation coefficients. The correlation coefficients did not reach the 5% significance level for any of the probe levels, though they came very close for the 57-dB probe sound pressure level (SPL).

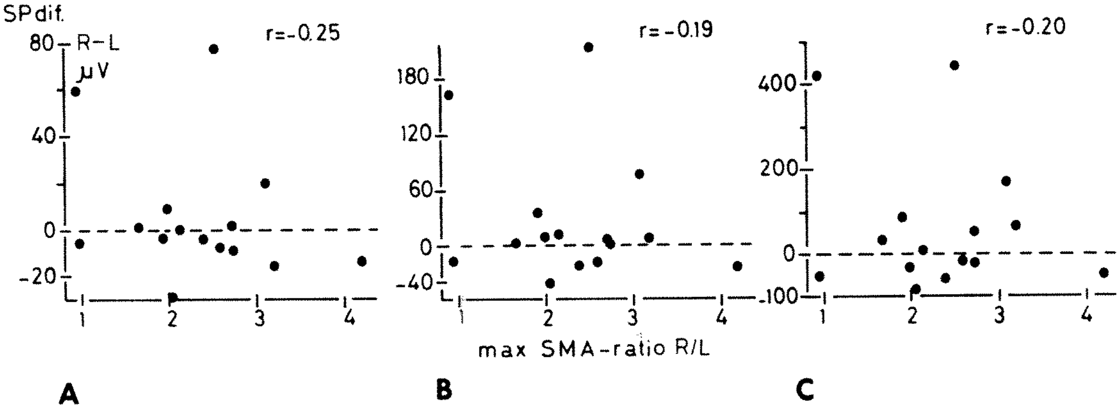

Fig 3. Scatterplots of difference in summating potential (SP) between right (operated) and left ear versus maximum scala media area (SMA) ratio for three levels of 8-kHz probe. Correlation coefficients are indicated in each plot. None of correlation coefficients was significant. A) 58 dB sound pressure level (SPL). B) 68 dB SPL. C) 78 dB SPL.

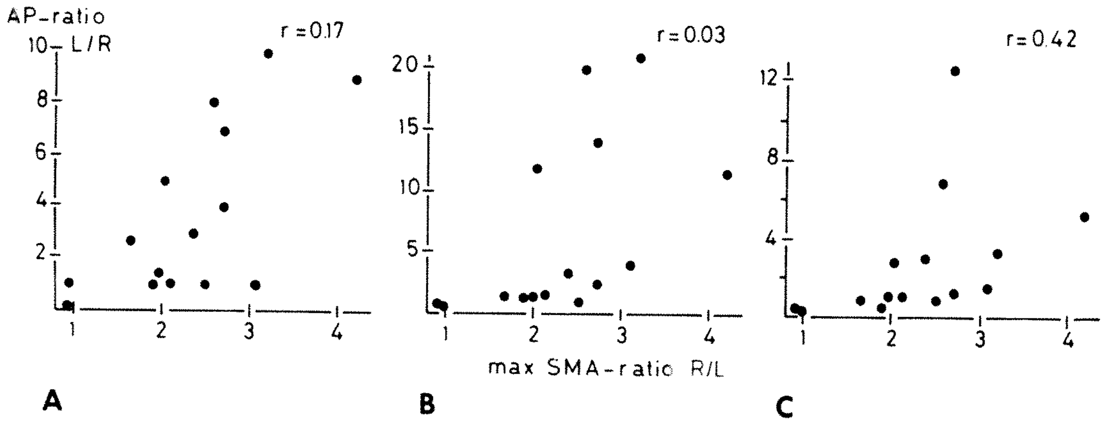

Fig 4. Scatterplots of ratio of compound action potential (AP left/AP right) versus maximum scala media area (SMA) ratio for three levels of 2-kHz probe. Correlation coefficients are indicated in each plot. None of coefficients was significant, though correlation coefficient for 57-dB probe sound pressure level (SPL) came very close. A) 37 dB SPL. B) 47 dB SPL. C) 57 dB SPL.

DISCUSSION

This paper describes a method for quantifying the degree of hydrops in ears that have endured endolymphatic duct obliteration. The degree of hydrops, expressed in the maximum SMA ratio, was correlated with electrophysiologic measures of functional changes in the operated ears.

A significant correlation was found between the degree of hydrops and the reduction in LFCM. This correlation decreases with increasing level of the low-frequency tone. The latter fact can be explained by saturation of the LFCM at high levels, where the LFCM from operated ears approaches that from the unoperated ears.[9] Two animals in this series were found to have a maximum SMA ratio of about 1. They showed a collapse of Reissner's membrane in the operated ears and also in one case an inexplicably large value for the LFCM ratio (the LFCM was larger in the operated ear). A reanalysis of the LFCM data excluding these two animals resulted in smaller correlation coefficients. However, the correlation coefficient was still significant at the 5% level when the LFCM level was 74 dB SPL.

Although there is a significant correlation between the maximum SMA ratio and the LFCM ratio, there is no such correlation between the maximum SMA ratio and the difference in SP between left and right ears. This suggests different mechanisms for both effects.

An endolymphatic hydrops probably exerts its effect on cochlear potentials through several physiologic intermediates. An important one is the decrease of the endocochlear potential.[13] Another may be endolymphatic overpressure, leading to distension of Reissner's membrane and probably also the basilar membrane.[14]

Overpressure in the endolymph may affect the movability of the basilar membrane. The correlation between distension of Reissner's membrane and reduction of the LFCM supports the hypothesis that overpressure in the endolymph is an important factor contributing to this reduction, provided that the distension of Reissner's membrane can be considered to be related to this hypothetical overpressure. The reduction of the endocochlear potential, as measured for instance by Kusakari et al,[13] is too small to fully account for the reduction of the LFCM.

Klis and Smoorenburg[15] suggested that the enlarged SP in hydropic guinea pig ears[7] and in some Meniere's patients might be caused by permanent displacement of the basilar membrane toward the scala tympani. Because there is no correlation between permanent displacement of Reissner's membrane and the magnitude of the SP, the results from this study suggest a more complex mechanism. The established reduction of the endocochlear potential[13] might be more important here. The SP is generally thought to consist of several components. If the SP is the resultant of a negative component that becomes smaller when the endocochlear potential becomes smaller, and a positive component that is not dependent on endocochlear potential, the resultant would become larger when the endocochlear potential becomes smaller. If the correlation between reduction of the endocochlear potential and distension of Reissner's membrane is weak, the correlation between magnitude of the SP and distension of Reissner's membrane would also be weak. Further research on both the nature of the SP and the relation between the various changes after endolymphatic duct obliteration is necessary to clarify this point.

The effect of endolymphatic hydrops on the AP could stem from both mechanisms described above: a reduction of the endocochlear potential and a reduced movability of the basilar membrane. Both would exert a deteriorative effect on the transduction process, of which the AP can be considered to be an end product.

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PERILYMPH FISTULA:
A COMMON CAUSE OF DIZZINESS AND DYSEQUILIBRIUM?

A conference entitled Perilymph Fistula: A Common Cause of Dizziness and Dysequilibrium? will be held Sept 6-8, 1990, in Portland, Oregon. For further information, contact Sharon Newman, Conference Coordinator, Dept of Neuro-otology, Good Samaritan Hospital and Medical Center, 1040 NW Twenty-Second Ave, Portland, OR 97210; (503) 229-7348.

Ann Otol Rhinol Laryngol 99:1990

EVOKED VERTEX AND INFERIOR COLLICULUS RESPONSES TO ELECTRICAL STIMULATION OF THE COCHLEAR NUCLEUS

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Evoked potentials were recorded from the vertex and the inferior colliculus in guinea pigs in response to electrical stimulation of the cochlear nucleus complex. The stimuli consisted of 80-μs biphasic pulses, ranging from 20 to 5,000 μA. The effect of electrode location (nerve root area, surface, and in-depth dorsal cochlear nucleus) on the evoked response was assessed by measuring amplitudes, latencies, and thresholds as a function of stimulating current levels. Stimulation of the nerve root area resulted in the shortest latencies, the largest amplitudes, and the lowest thresholds, whereas the surface of the dorsal cochlear nucleus was the least effective stimulating site.

KEY WORDS — cochlear nucleus, electrical stimulation, evoked responses, guinea pig, inferior colliculus.

INTRODUCTION

Investigation of the cochlear nucleus complex (CNC) as a possible site for an auditory prosthesis is an important step in the development of artificial means of stimulating the auditory pathways of the profoundly deaf. This is especially relevant in cases in which there is damage to or absence of spiral ganglion cells and the most peripheral access to the central auditory pathways is at the level of the cochlear nuclei.

Previous studies have demonstrated behavioral responses to electrical stimulation of the CNC in humans[1] (also D. L. Eskwitt, A. A. Maltan, W. House, unpublished presentation, September 1987) and in cats,[2,3] indicating that it is possible to activate central pathways in this manner. This study examines the effect in guinea pigs of electrical stimulation of the CNC on evoked activity recorded from the vertex and the inferior colliculus (IC). The objectives are to assess the effectiveness of electrode location and bipolar configuration by measuring 1) the threshold current level required for activation of central pathways, 2) the amplitudes and latencies, and 3) the dynamic range of activation of evoked potentials.

METHODS

Twenty-five pigmented guinea pigs weighing between 250 and 350 g were used in this experiment. The animals were anesthetized with ketamine hydrochloride (120 mg/kg) and xylazine (16 mg/kg) administered intramuscularly in a 3:2 mixture. Regular supplementation was used to maintain anesthetic levels. The CNC was visualized after a posterior fossa opening and aspiration of the overlying cerebellum. Stimulating electrodes were placed under visual control with use of a dissecting microscope onto one of two possible "surface" locations: 1) the dorsal cochlear nucleus (DCN) and 2) the nerve root area (NRA). For the latter position, the electrode was placed between the bone lateral to the posterior ventral cochlear nucleus and the lateral surface of the posterior ventral cochlear nucleus. In neither case did the electrode penetrate the surface of the structure. For assessment of in-depth stimulation of the DCN, electrodes were placed on the surface of the DCN and advanced from outside a double-walled sound booth with use of a Burleigh Inchworm, model PZ-550, remote-controlled piezoelectric microdrive; the electrode was advanced in a dorsoventral direction in 100-μm steps. After electrode placement, the brain was covered with warm mineral oil to prevent tissue decussation and reduce brain pulsation. Body temperature was maintained near 38°C with use of a rectal probe to sense core temperature and a feedback circuit to drive a heating blanket.

A constant-current stimulator that produced biphasic (40 μs per phase) pulses was used as the current source. The initial stimulus phase was positive. Stimuli were presented at a rate of 20/s. Current was passed between two wires of a five- or two-wire platinum-iridium (10% alloy) electrode with wire diameters of 125 μm for surface, or 175 μm for in-depth stimulation. The horizontal distances between electrodes varied between 125 and 250 μm. The electrodes were insulated with Teflon except for the contact points. Typical impedances of these types of electrodes range from 14 to 20 kΩ.

Vertex potentials were recorded from a stainless steel screw electrode screwed into the vertex through the skull to contact dura. Reference elec-

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From the Kresge Hearing Research Institute and the Department of Electrical Engineering and Computer Science, University of Michigan, Ann Arbor, Michigan (all authors); and the Department of Otolaryngology, Medical College of Ohio, Toledo, Ohio (Shore). Supported by grant NO1-NS-5-2387 from the National Institutes of Health. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Michigan.

REPRINTS — Susan E. Shore, PhD, Kresge Hearing Research Institute, 1301 E Ann, Ann Arbor, MI 48109.

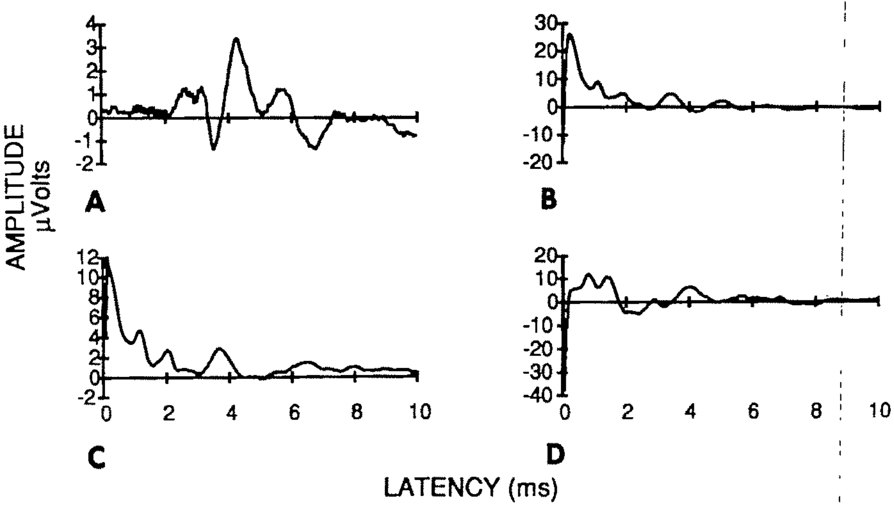


Fig 1. Averaged potentials evoked A) by acoustic stimulation at vertex, B) by electrical stimulation of nerve root area at vertex, C) by electrical stimulation of nerve root area at inferior colliculus, and D) by electrical stimulation of dorsal cochlear nucleus at inferior colliculus.

trodes were placed subcutaneously in the tissue overlying the mastoid region ipsilateral to the side of stimulation. The leads were connected to the input of a differential, Grass model P15, preamplifier with 0.1-Hz to 50-kHz band-pass filtering with 1,000x gain. An additional 100x gain homebuilt amplifier, with 0.5-Hz to 30-kHz band-pass filtering, was attached in series to the output of the P15 preamplifier, producing a total gain of 100,000x. The amplified signal was fed into a Modular Instruments Incorporated A-to-D conversion module programmed to operate with an IBM/AT computer. A trigger synchronized to the current pulse was used to trigger the averaging program. A low-noise signal was obtained with an average of 1,024 sweeps; there were 100 samples per trial, with a sample frequency of 10 kHz and sample duration of 10 ms. Stimulus artifact was reduced by use of the artifact reject feature in the data acquisition program, which could be adjusted to reject large-amplitude waveforms from the averaging procedure. Some artifact may have remained in the response signal, possibly producing some distortion of the early latency values. However, we feel confident that the peaks are true "neural" peaks, because their growth with increased stimulus amplitude is nonlinear.

Inferior colliculus potentials were obtained with a silver wire electrode placed on the brachium of the contralateral IC after aspiration of a small portion of the overlying cortex. Reference electrodes were the same as those for the vertex potentials.

Auditory brain stem responses (ABRs) to a 10-kHz tone pip (3-ms duration with a 0.05-ms rise/fall) were often recorded in addition to the electrically evoked potentials (EABRs). The acoustic signals were transduced by a TDH-39 earphone coupled to a tapered plastic tube, which was inserted into the external meatus to produce a closed acoustic system. The length of the tube was 1.3 cm, producing an additional time delay of 38.77 µs. Sound pressure level (SPL) was measured with a probe tube inserted into the external auditory meatus and coupled to a measuring amplifier. Electrode configurations were the same as for the vertex EABRs. Electrical and acoustic stimuli were presented at levels ranging from those that evoked threshold responses to the limits of the instrumentation. For acoustic stimuli the limits corresponded to 120 dB SPL, and for electrical stimuli, to saturation and distortion of the output signal due to maximal current delivery. Above this value, it was assumed that the source voltage was insufficient to produce the desired current. Of the 25 animals used for these experiments, 16 were used for surface stimulation, 6 of which received both electrical and acoustic stimulation. The other 9 animals were used for in-depth stimulation, 4 of which received both electrical and acoustic stimulation. The EABR and ABR recordings were taken in random order for each animal, as were the IC and vertex recordings. Animals in which repeat measures indicated damage or a deteriorated preparation were eliminated from the analysis. In some animals, high current levels produced muscle twitching. These animals were also eliminated from the analysis.

RESULTS

Electrical stimulation of the CNC resulted in evoked potentials with four clearly observable peaks, recorded from the vertex and IC. Sometimes five or six peaks were observed, but the latter peaks were attributed to muscle artifact as described by van den Honert and Stypulkowski.[4] Figure 1A shows the waveform of an acoustically evoked vertex ABR. For comparison, an NRA EABR recorded at the vertex is shown in Fig 1B, and one recorded at the IC in Fig 1C. The waveforms of the vertex and IC potentials were very similar, both with four positive peaks and interpeak latencies similar to those of the acoustically evoked responses. Waveforms from the IC obtained in response to DCN stimulation also showed four peaks (Fig 1D), but differed morphologically from those recorded in response to NRA stimulation.

TABLE 1. MEAN LATENCIES OF POTENTIALS

Peak	*Dorsal Cochlear Nucleus (ms)*	*Nerve Root Area (ms)*
Vertex		
1	0.254	0.259
2	0.933	1.150
3	1.880	2.045
4	3.244	3.450
Inferior colliculus		
1	0.131	0.194
2*	1.187	0.837
3	2.167	2.175
4	3.475	3.260

*Significant at $p<.1$.

Collicular potentials showed the same differences for site of stimulation as did the vertex potentials. However, in many cases IC potentials were more readily obtained than vertex potentials, and there were animals in which IC potentials could be obtained in the absence of evoked vertex potentials.

Response Latencies. Mean latencies of each peak of the vertex and IC potentials recorded in response to DCN and NRA stimulation are shown in Table 1. The latencies were measured from pulse onset for stimulus values 200 μA above threshold for the electrical stimulation, and at 20 dB above threshold for acoustic stimulation. Mean latencies for all peaks of the vertex potentials were longer for acoustic stimulation than for electrical stimulation at either location. The mean latencies for peak 2 of the DCN-evoked IC potentials were significantly longer than those evoked by NRA stimulation ($p<.1$, Table 1). Interpeak latencies have been shown previously to be a reliable indicator of the activation of successive generators along the brain stem.[5,6] Interpeak latencies for IC potentials were significantly longer between peaks 1 and 2 with DCN stimulation than NRA stimulation (Table 2), while the latencies between peaks 2 and 3 were significantly shorter for DCN stimulation ($p<.1$, Table 2).

TABLE 2. INTERPEAK LATENCIES FOR POTENTIALS

Peaks	*Dorsal Cochlear Nucleus (ms)*	*Nerve Root Area (ms)*
Inferior colliculus		
1-2	1.025	0.637
1-3	2.033	1.975
1-4	3.344	3.120
2-3	0.850	1.483
2-4	2.275	2.500
3-4	1.325	1.200
Vertex		
1-2	0.700	0.925
1-3	1.640	1.850
1-4	3.028	3.233
2-3	0.767	0.900
2-4	No peak seen	1.975
3-4	1.450	1.469

Electrode Configuration. In the initial experiments a five-wire platinum-iridium electrode was used to estimate the most effective horizontal distance between bipolar stimulating wires. Figure 2 shows the amplitudes and latencies of peak 3 of the IC potentials obtained with the stimulating electrode on the DCN. The three curves represent stimulation with distances of 0.33 mm, 0.66 mm, and 0.99 mm between stimulating electrodes. The most closely spaced electrodes resulted in lower-threshold, higher-amplitude, and shorter-latency responses at all current levels tested.

Dynamic Range of Response. Thresholds for surface DCN stimulation were generally high, above 200 μA, and the dynamic range was small. Maximum amplitudes of the evoked vertex potentials were around 10 μV. Figure 3 shows an example of the amplitudes and latencies of peaks 1 and 3 of the vertex potentials recorded during DCN and NRA stimulation. In contrast to the DCN, stimulation of the NRA resulted in lower threshold responses with a much wider dynamic range. Threshold responses were often obtained at the lowest current level produced by our stimulator (20 μA); amplitudes could reach 120 μV. Latency showed complex changes with increases in current level, sometimes decreas-

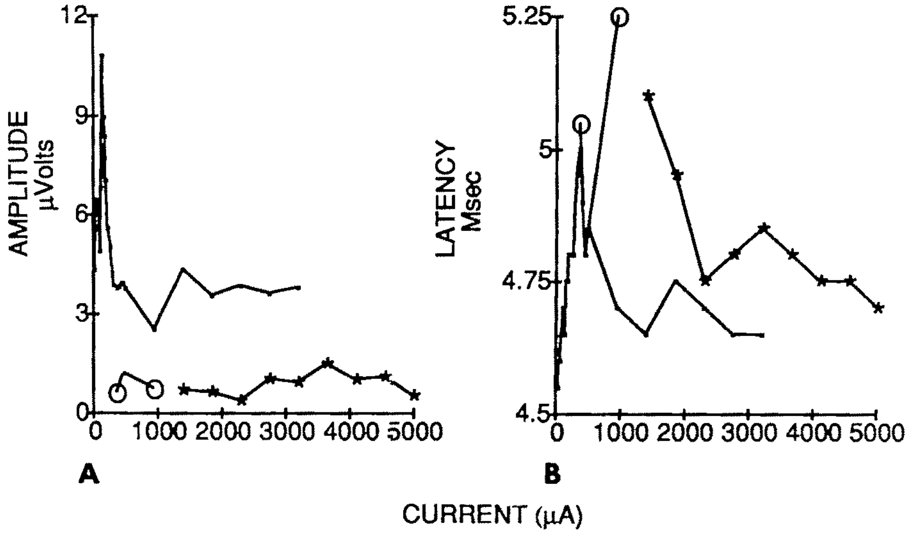


Fig 2. Peak 3 A) amplitudes and B) latencies for inferior collicular potentials obtained from dorsal cochlear nucleus stimulation for different interelectrode distances. Dots — 0.33 mm, circles — 0.66 mm, asterisks — 0.99 mm.

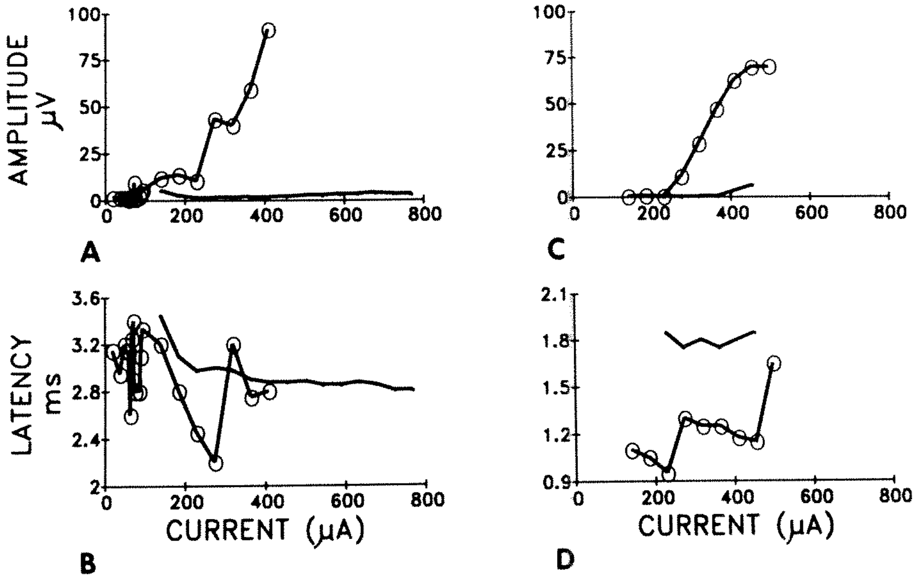


Fig 3. Amplitudes and latencies for peak 3 (A,B) and peak 1 of a different animal (C,D) of vertex potentials recorded during dorsal cochlear nucleus (dots) and nerve root area (circles) surface stimulation.

ing and sometimes increasing before reaching a steady state. It was often possible to evoke potentials with the NRA stimulation where DCN placements were unsuccessful.

In-depth Stimulation of Dorsal Cochlear Nucleus. The evoked potentials measured as the stimulating electrodes were advanced in a dorsoventral direction showed distinct and reliable changes in amplitude and latency. Figure 4 shows the growth in amplitude of peak 3 of the IC potential as current level is increased. Potentials recorded at several stimulating electrode depth locations are shown. Figure 5 shows peak 3 amplitude growth as a function of stimulating electrode depth for one current level (500 µA). Amplitude increased up to a depth of about 700 µm, below which it began to decrease. Figure 6 shows examples of this effect from another animal with a comparison of five repeat measures at one depth, emphasizing the reliability of the changes shown in the previous figures.

DISCUSSION

From these studies, it is apparent that the central auditory pathways can be activated by means of biphasic, constant current stimulation with bipolar electrodes placed on the surface of the CNC. The thresholds, latencies, and amplitudes of the evoked activity vary depending on the distance between stimulating electrodes and the electrode placement. More closely spaced electrodes on the surface of the DCN produced lower threshold responses, probably reflecting the larger current density produced by the closer spacing. It appears that the most effective stimulating site is the NRA. In addition to thresholds being lower for this area than for the DCN, it is often possible to evoke activity in this region when no response is obtained from other regions.

It is known that stimulation of large, myelinated axons generally occurs at lower levels than stimulation of the somas of neurons. On this basis, the NRA stimulation site would be expected to have lower thresholds than the surface of the DCN. With the correct electrode orientation, however, it may be possible to stimulate fibers of the dorsal acoustic stria that run close to the surface of the DCN.[7] Another possible advantage of the NRA as a stimulation site is that a more nearly normal activation of the auditory pathways via the incoming nerve fibers could occur, whereas activation of the DCN alone could result in selective stimulation of only part of

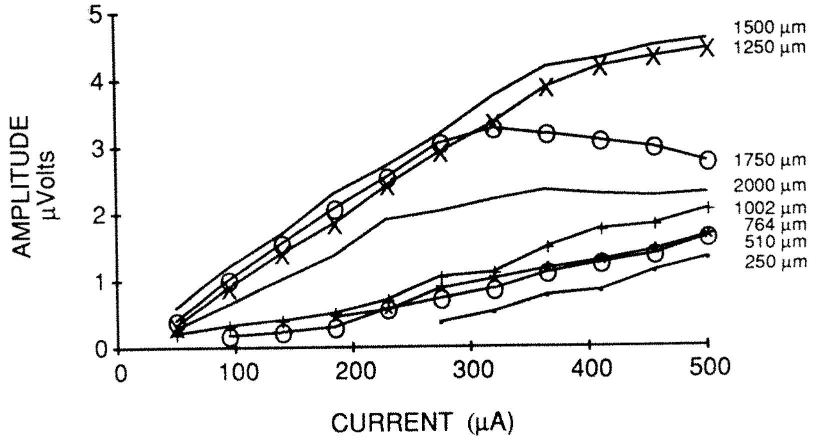


Fig 4. Inferior colliculus responses obtained at several depths as dorsal cochlear nucleus stimulating electrode advanced in dorsoventral direction. Growth in amplitude of peak 3 with increasing current is seen.

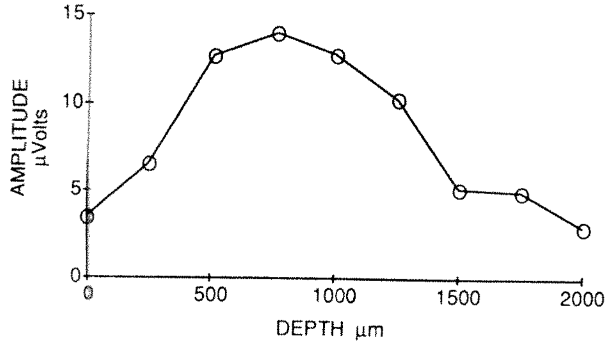


Fig 5. Peak 3 amplitude growth of inferior colliculus potential as function of stimulating electrode depth for one current level (500 μA).

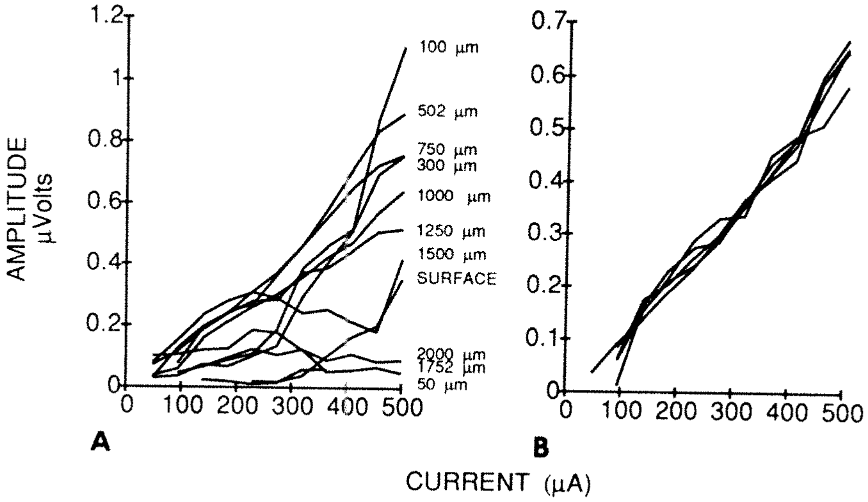
the outgoing innervation to higher centers.[7] Caution should be used in the development of a prosthesis designed for a DCN stimulation site. There is growing information on different functional subgroups of cells in the DCN that suggests that different pathways may be activated with DCN stimulation than with either NRA or acoustic stimulation. The differences in interpeak latencies obtained with NRA and DCN stimulation support this contention.

One reason for lack of success in evoking responses in some animals could be the generation of "anodal block." That is, the hyperpolarizing anodal surround caused by inward current is larger than the depolarizing outward current and prevents propagation of the action potential.[8] Studies with peripheral nerve fibers[9] and CNC showed that currents from an extracellular cathode, which are much higher than current required for threshold, would fail to elicit a propagated action potential. An alternative reason for failure to evoke responses from the DCN could be the orientation of the electrode with respect to fiber bundles. If the bipolar electrodes are longitudinal, and therefore the current gradient is transverse to fibers running through the DCN, greater current levels would be required to reach threshold, since if the extracellular voltage gradient is entirely transverse to an axon, the axon cannot be stimulated.[10] There is a zero potential plane midway between the electrode pair that eliminates the potential difference along the neuron required to produce current flow.[11] In the NRA, the electrode voltage gradient may be longitudinal to the eighth nerve fibers, an orientation that allows the neuron to receive full benefit of the current radiating from the end of the bipolar electrode.[11]

The variation in threshold observed both within and across sites of stimulation may be due to differences in fiber diameter, cell membrane properties, and distributions of nodes of Ranvier in relation to the electrical field. The larger dynamic range observed for NRA stimulation compared to DCN stimulation, where the growth of amplitude reaches a plateau at about 80 μA, probably reflects the proximity of the electrode to the target subpopulation, since this maximizes the relative distance to the remainder of the population.[8,11,12]

Results of the in-depth stimulation study suggest that the amplitudes and latencies of the evoked potentials can provide information about which neural pathways are activated by different stimulating electrodes. The progressive increase followed by a large decrease in amplitude at specific depths is consistent with anatomic locations of cell types within the DCN.[13-15] Specifically, at the surface of the DCN, the electrode is likely to be stimulating granule cells and their parallel fibers, which are oriented transverse to the extracellular voltage gradient produced by the electrode. This orientation would require large voltages for depolarization. Below the surface, different cell types may be stimulated that would contribute to the amplitudes of the evoked potential. In one case (Fig 6A) maximum amplitude occurred at 100 μm, closer to the surface than in most other animals. Possibly, the mediolateral location of this electrode activated fusiform cells near the surface of the nucleus. Amplitudes of evoked potentials begin to increase at a depth corresponding to the eighth nerve–fusiform cell synapse (500 to 1,500 μm; J. K. Moore, personal communication, 1989). Maximum amplitudes are pro-

Fig 6. Peak 3 amplitude. A) Growth of amplitude as function of stimulating current for different electrode depths. B) Five repeat measures, shown to emphasize reliability of changes for depth of 1,000 μm.



duced at depths at which the descending branch of the eighth nerve enters the DCN (below 1,500 μm). The orientation of the fibers here is longitudinal to the electrode voltage gradient, theoretically enabling easy depolarization. As the electrode is advanced below this point and eventually out of the nucleus, current levels required for depolarization again increase.

The descending branch of the eighth nerve terminates predominantly on the basal dendrites and somas of fusiform and giant cells, which in turn send axons centrally via the dorsal acoustic stria to the IC. The afferents of the eighth nerve also contact small and granule cells within the DCN, which are thought to be intrinsic neurons.[5,15] The difference in interpeak latencies of the evoked potentials between DCN and NRA stimulation suggests different pathways of activation. In addition to activation of the fusiform/giant cell–dorsal acoustic stria system, it is possible that retrograde excitation of the ascending branch of the eighth nerve could result in activation of ventral cochlear nucleus cells and the ventral and intermediate acoustic stria. It is therefore not surprising that NRA stimulation produces evoked potentials that show a closer correspondence to those evoked by acoustic stimulation.

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PRIMARY LYMPHOPLASMACYTIC LYMPHOMA OF THE LARYNX: A RARE LOCALIZATION OF MALT-TYPE LYMPHOMA

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Laryngoscopy carried out in a 46-year-old man revealed a left paralaryngeal tumor. The mass was entirely removed by left pharyngolaryngotomy. Microscopic study showed a diffuse malignant lymphoma of low-grade malignancy, exhibiting all the criteria of the MALT-type lymphoma: the proliferation of centrocyte-like and lymphoplasmacytic cells, lymphoepithelial lesions, and the presence of germinal centers. Primary lymphoma of the larynx is a rare condition. Most of the reported low-grade lymphomas and the pseudolymphomas probably belong to the category of MALT-type lymphoma. Remission can be obtained by surgery, radiotherapy, and polychemotherapy.

KEY WORDS — lymphoma, mucosa-associated lymphoid tissue, tumor.

Primary non-Hodgkin's lymphoma limited to the larynx is a rare form of lymphoma. The case we report showed histologic evidence of malignant lymphoma of mucosa-associated lymphoid tissue (MALT), as defined recently by Isaacson et al[1-3] and Michael and Isaacson.[4] Comparison with previously published cases seems to demonstrate that most of the primary low-grade lymphomas limited to the larynx could belong to the MALT lymphoma group.

CASE REPORT

A 46-year-old man who was a heavy smoker had been suffering from dysphonia for a year. He underwent a laryngoscopy in January 1988, revealing the presence of a submucosal laryngeal tumor that consisted of a left paralaryngeal mass. No other tumor was found in the cavum or in the Waldeyer's ring lymphoid tissue. Laryngeal tomography and scanner exploration confirmed the existence of the left paralaryngeal tumor and demonstrated its extension into the glottic and supraglottic regions with no involvement of the left vocal cord.

The findings on physical examination were normal: no cervical or other peripheral lymphadenopathy, and no hepatosplenomegaly. There was no history of fever, night sweats, or weight loss. Laboratory data were as follows: hemogram, normal; fibrinogen, 3.5 g/L; α-2-globulin, 6 g/L; LDH, 168 (normal level).

In March 1988, a left pharyngolaryngotomy was performed and the mass completely removed. Following the histopathologic diagnosis, further evaluation included a chest x-ray, thyroid scintigraphy, esophagogastrofibroscopy with gastric biopsies, an abdominal scan, and a bone marrow biopsy. All these investigations failed to reveal the presence of other tumor localizations.

The final diagnosis was non-Hodgkin's lymphoma limited to the left part of the larynx, with a clinical staging of IEa, of a histologically low-grade centrocytic and lymphoplasmacytic MALT type.

Treatment consisted of six courses of polychemotherapy protocol (cyclophosphamide, vindesine, prednisone), followed by locoregional radiotherapy at a dose of 40 Gy.

PATHOLOGIC FINDINGS

The gross specimen consisted of a soft homogeneous mass, localized in the submucosa, between a normal respiratory epithelium and a normal thyroid cartilage, with an extension into the hyothyroepiglottic space with no involvement of the vocal cord. The tumor measured 4 x 2.5 cm and was totally resected by the partial hemilaryngectomy.

At the histologic level, there was a diffuse infiltrate extending from the mucosa to the thyroid cartilage (see Figure, A). In this diffuse infiltrate, some germinal centers could be recognized. They appeared normal, with nests of hypertrophied dendritic reticulum cells (see Figure, B).

This infiltrate was composed of a mixture of small lymphoid cells with slightly irregular, more or less cleaved nuclei and a pale cytoplasm, small lymphocytes with round nuclei, and lymphoplasmacytic cells (see Figure, C). Some large cells with basophilic cytoplasm (immunoblasts) were dispersed in the diffuse sheets of cells. Rare small clusters of epithelioid cells were also revealed. Glandular lobules were surrounded by the tumor infiltrate. In some glands, nests of tumor lymphoid cells were identified between the epithelial cells, creating so-called "lymphoepithelial lesions" (see Figure, D).

The cell morphology, the diffuse infiltrate associated with normal germinal centers, and the lymphoepithelial lesions were considered as evidence

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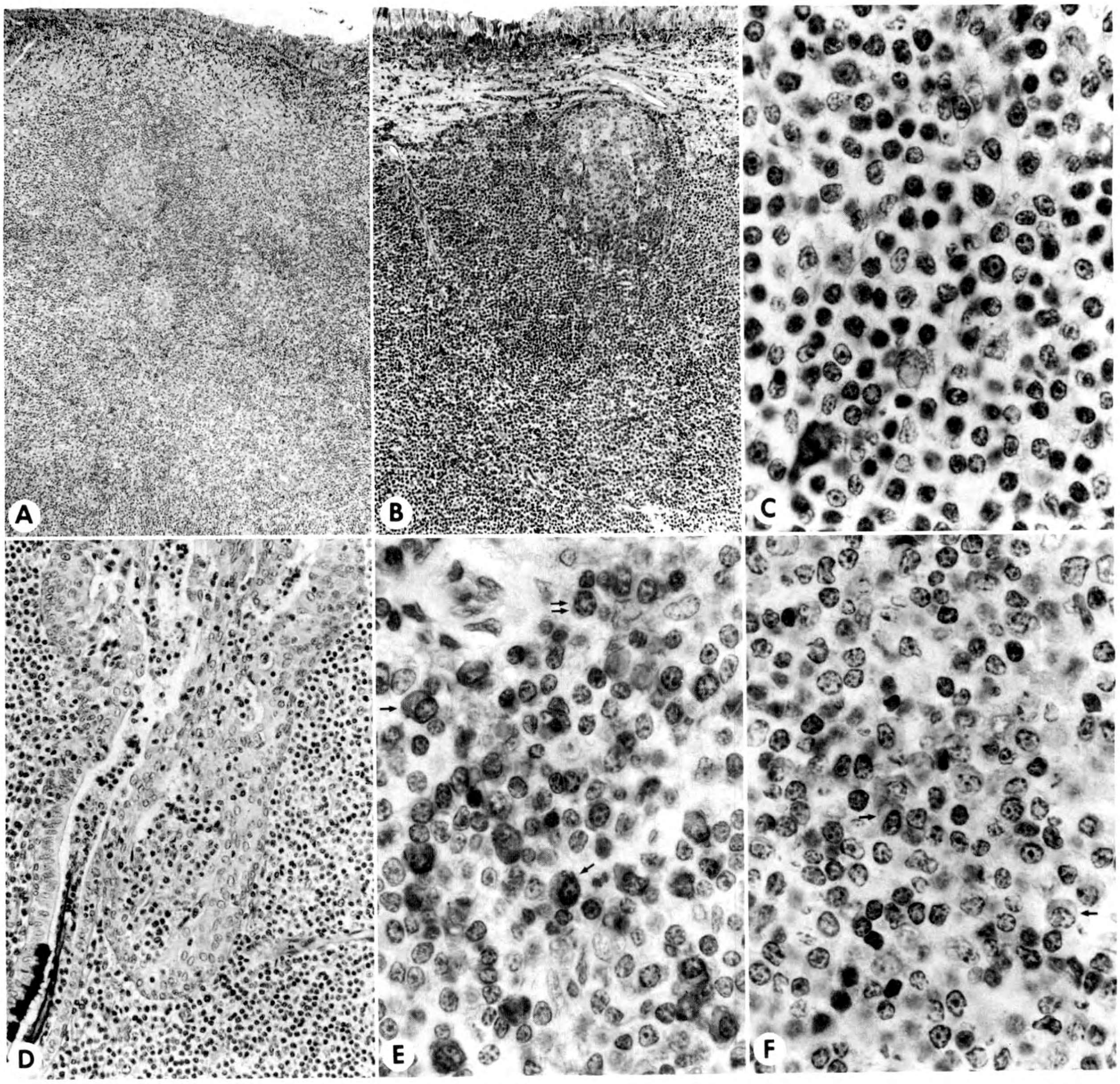

Histologic photomicrographs. A) Diffuse infiltrate with follicles (H & E, original x80). Note absence of ulceration of epithelium. B) Follicle with reactive germinal center surrounded by lymphomatous infiltrate (Giemsa, original x190). Epithelium is normal. C) Infiltrate comprising small lymphoid cells with slightly irregular nuclei (centrocyte-like), plasma cells, and lymphoplasmacytoid cells (H & E, original x900). D) Lymphoepithelial lesion characterized by clusters of lymphomatous cells between epithelial cells of glands. E,F) Immunolabeling with immunoperoxidase on paraffin section (original x850). Cytoplasmic positivity for E) α chain and F) $\varkappa$ chain in plasma cells (arrows) and lymphoplasmacytoid cells (double arrows).

for the diagnosis of low-grade malignant lymphoma of the lymphoplasmacytic and centrocyte-like MALT type, according to the description given by Isaacson et al[1-3] and Michael and Isaacson.[4]

IMMUNOHISTOCHEMICAL FINDINGS

This examination was performed according to an immunoperoxidase method with an avidin biotin complex amplification procedure. Polyclonal antibodies that recognize light and heavy chains of immunoglobulins were used.

The tumor population was positive, with anti-IgA and anti-$\varkappa$ light chain antibodies (see Figure, E,F). The lymphoplasmacytic cells exhibited cytoplasmic positivity. Some positive intranuclear inclusions were also discovered. At the periphery of the tumor infiltrate and beneath the mucosa, a few polytypic mature plasma cells secreted mainly IgG and IgM. These results confirmed the lymphoplasmacytic component of the lymphoma.

DISCUSSION

Primary lymphomatous involvement of the larynx is a rare condition. The first described case can be attributed to MacKenty[5] in 1934, as reported by Remacle et al[6] in their review. These authors also mention two earlier cases briefly cited in the literature, one seen by Stoerck in 1895, another by Tanturri in 1932.[6] They list 79 cases published prior to 1986. Since then, three other cases have been published.[7-9] Including the present case, the total number of reported primary lymphomas of the larynx now seems to be 83.

According to Remacle et al,[6] the median age of patients is 62 years, with ages ranging from 4½ to 81 years. These lymphomas are predominantly found in the male population. The lymphoma is often localized to one side of the larynx, with a predominantly supraglottic localization, with or without glottic or subglottic involvement. In most cases, as in our own, laryngoscopy reveals a regular submucosal mass with a smooth surface and no ulceration. In the majority of published cases it has not been possible to determine the exact histologic type of the lymphoma. One thing does seem clear: both small cell (low-grade malignancy) and large cell (high-grade) lymphomas have been described. Only a few of the cases can be interpreted in terms of either the Kiel classification[10] or the Working Formulation.[11] Swerdlow et al[12] reported one case classified as diffuse small cleaved lymphoma. Ferlito et al[13] reported three cases of diffuse lymphomas classified respectively as large cleaved, small cleaved, and large noncleaved follicular center cells. Ten other cases of low-grade lymphoma can be identified: one malignant lymphoma of low differentiation,[14] one low-grade malignant lymphosarcoma,[15] three lymphocytic lymphosarcomas,[16] one diffuse mixed lymphoma,[16] and four lymphocytic lymphomas.[8,17,18] Only one case of high-grade lymphoma can be identified as centroblastic or large noncleaved lymphoma.[6] In all the other cases, information, description, and denomination are not precise enough to allow correct classification.

The presently reported case exhibits all the features described in low-grade malignant lymphomas arising in MALT: the association of monotypic lymphoplasmacytic and centrocyte-like cells, and the presence of lymphoepithelial lesions and reactive germinal centers.[1-4,19]

There is some evidence that most of the primary low-grade non-Hodgkin's malignant lymphomas, such as ours, belong to this MALT-type lymphoma. First, the histologic type of some published cases corresponds exactly to the cell type seen in MALT lymphoma,[12,13] or is compatible with this diagnosis.[8,14-18] Second, remission and a good prognosis can be obtained through surgery and radiotherapy.[6] Third, the origin of the lymphoma, which probably develops, as suggested by Swerdlow et al,[12] in the lymphoid collection of the supraglottic lamina propria and laryngeal ventricles, is another argument in favor of this hypothesis. Finally, in some cases, there is evidence of the involvement of another MALT area in the course of the disease. For example, in one patient, an orbital lymphoma was discovered 25 months after the laryngeal lymphoma[16]; and in another patient with primary lymphoma of the breast of the MALT type, secondary laryngeal involvement was discovered.[20]

Primary low-grade malignant lymphoma of the larynx has another particularity in common with the MALT type of lymphoma. Both were often misdiagnosed in the past as pseudolymphoma. This was seen especially in stomach, lung, and salivary gland lymphomas.[1-4,19] The similarity between some primary lymphomas of the larynx and pseudolymphomas was stressed by Swerdlow et al.[12] Pseudolymphomas of the larynx are described as rare lesions that may mimic lymphoma both grossly and microscopically.[21,22] The differentiation from true lymphoma is made according to the following histologic features: the presence of a mixed cellular infiltrate composed of lymphocytes, plasma cells, and histiocytes, and the presence of true germinal centers.[9,12,21,22] According to the histologic description of the eight cases published in the literature and summarized by Pellettiere et al,[22] it seems quite possible that most of the so-called pseudolymphomas of the larynx could be true primary lymphomas of the MALT type.

In conclusion, we have reported a case of primary lymphoma of the larynx exhibiting the histologic features of monotypic $\alpha\kappa$ lymphoplasmacytic and centrocyte-like lymphoma of the MALT type, as described by Isaacson et al[1-3] and Michael and Isaacson.[4] Comparison with other published cases of primary lymphoma of the larynx and so-called pseudolymphoma of the larynx supports the hypothesis that most laryngeal lymphomas belong to the MALT group.

ACKNOWLEDGMENT — We thank Maurice Wolfelsperger for the photographs.

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Ann Otol Rhinol Laryngol 99:1990

BETA-ADRENOCEPTOR CONTROL OF PEROXIDASE SYNTHESIS IN NASAL GLANDS

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Endogenous peroxidase activity was observed in the cisternae of the rough-surfaced endoplasmic reticulum (r-ER), including the nuclear envelope, Golgi complex, and secretory granules of the cat's nasal glands. A single injection of propranolol resulted in a decrease of peroxidase-positive secretory granules, an increase of electron-lucent granules, and no change in the level of peroxidase activity in the r-ER and Golgi complex at either 5 or 9 hours after the injection. Continuous administration of propranolol over 7 hours led to the disappearance of peroxidase activity from the r-ER and secretory granules. These data would indicate that propranolol inhibits only the synthesis of peroxidase. Twenty minutes after a single injection of isoproterenol, the rate at which the granule content containing the peroxidase reaction product was discharged into the acinar lumen increased sharply. However, 60 minutes after the injection, the secretion rate of peroxidase-positive granules decreased. The same experiment then was repeated, but this time before the isoproterenol was injected, propranolol was administered to the cats. This time no change in peroxidase activity appeared in the acinar cells. It was concluded, therefore, that the stimulation of β-receptors enhances the synthesis of peroxidase.

KEY WORDS — β-receptor, isoproterenol, nasal glands, peroxidase, propranolol.

INTRODUCTION

In a previous study we reported that endogenous peroxidase was present in human nasal glands.[1] It is considered to have virucidal[2] and bactericidal[3] roles, but as the activity of this enzyme diminishes in patients with nasal allergies,[1] it is likely also to be related to allergy, and especially to the autonomic nervous system. It is therefore possible to understand the autonomic nervous system of the nasal mucosa by studying the peroxidase activity. We speculated that the synthesis of this enzyme was enhanced by a β-stimulant, because the endogenous peroxidase activity in the tracheal epithelium,[4] which is situated in the upper respiratory airway as well as nasal glands, was decreased by the administration of propranolol (β-blocker).[5] Subsequently, we have discovered that this same enzyme is to be found in the nasal glands of cats. In the present experiment using common house cats we investigated the changes of peroxidase activity in the acinar cells of nasal glands through the administration of propranolol and isoproterenol.

MATERIALS AND METHODS

Twelve cats weighing 3 to 3.5 kg were used as experimental animals. They were anesthetized intraperitoneally with pentobarbital in doses of 35 mg/kg. Propranolol (β-blocker) or isoproterenol (β-stimulant) was injected in four different protocols. 1) Propranolol was administered intravenously by a single injection to three cats in doses of 7.3 mg/kg. Nasal mucosa was removed before the administration, and at 30 minutes, 5 hours, and 9 hours after the administration. 2) Propranolol was administered intravenously continuously over 7 hours to three cats in doses of 8 mg/kg dissolved in 300 mL of physiologic saline solution. Nasal mucosa was removed at the end of the 7 hours. 3) Isoproterenol was administrated intravenously by a single injection to three cats in doses of 0.3 mg/kg. The nasal mucosa was removed before the administration, and at 20 minutes and 60 minutes after the administration. 4) Ten minutes after intravenous injection of 7.3 mg/kg of propranolol, 0.3 mg/kg of isoproterenol was administered intravenously to three cats. Nasal mucosa was removed 20 minutes and 60 minutes after the isoproterenol injection. In every animal, specimens were removed from an anterior portion of the inferior turbinate.

These samples were fixed at 4°C for 1 hour in 2% glutaraldehyde fixative and then were washed three times with 0.1 mol/L cacodylate buffer (pH 7.2) containing 8% sucrose. Thick slices (40 μm) were cut with a tissue sectioner (Sorvall TC-2). The tissue slices were incubated for 1 hour at room temperature in a modified Graham-Karnovsky medium[6] (0.05 mol/L Tris-HCl buffer with a pH of 7.1 in an amount of 10 mL containing 0.002% H_2O_2 and 8 mg of 3,3′-diaminobenzidine tetrahydrochloride). As reaction controls, the samples were incubated in a medium lacking H_2O_2 and containing 10^{-2} mol/L potassium cyanide. The samples were further fixed for 50 minutes in 2% OsO_4 and embedded in Epon 812. Ultrathin sections for electron microscopic observation were cut with a Porter Blum Type II ultramicrotome. They then were stained with lead citrate and examined by transmission electron microscopy.

RESULTS

SAMPLES BEFORE ADMINISTRATION OF DRUGS (CONTROL) (FIG 1)

The reaction products of peroxidase in nasal

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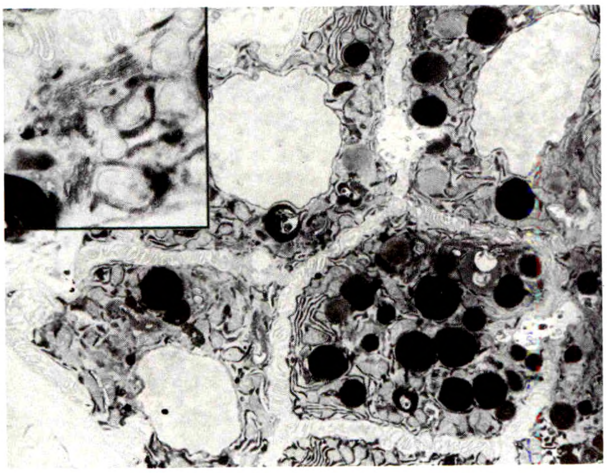

Fig 1. Acinar cells before administration of drugs (control) (original x7,000). Reaction product of peroxidase was observed in r-ER, Golgi complex (inset [original x24,000]), and secretory granules. Only few secretory granules showed little or no peroxidase activity.

glands were observed in the rough-surfaced endoplasmic reticulum (r-ER), including the perinuclear envelope, some saccules of the Golgi complex (inset), which revealed a weaker reaction than the r-ER, and the secretory granules. The dense deposits of the reaction product were observed in almost all the secretory granules. A few secretory granules were stained either slightly or not at all.

ADMINISTRATION OF PROPRANOLOL

Propranolol was administered in doses of 7.3 mg/kg by a single injection.

Thirty Minutes After Administration of Propranolol (Fig 2A). The activity and localization of peroxidase were almost the same as in the controls. The electron density in the r-ER, Golgi complex, and secretory granules was the same as shown in Fig 1.

Five Hours After Administration of Propranolol (Fig 2B). The peroxidase reaction products were observed in the perinuclear envelope, r-ER, Golgi complex, and secretory granules, but the number of granules with a high electron density decreased. There was an increase in electron-lucent secretory granules.

Nine Hours After Administration of Propranolol (Fig 2C). Though the peroxidase reaction products were observed in the r-ER and Golgi complex, secretory granules without peroxidase activity were increasingly observed. Very few secretory granules showed any peroxidase activity.

CONTINUOUS INTRAVENOUS ADMINISTRATION OF PROPRANOLOL

Propranolol was administered in doses of 8 mg/kg over 7 hours (Fig 3). Peroxidase activity decreased in the acinar cells of the nasal glands. In a small number of the acinar cells peroxidase activity was

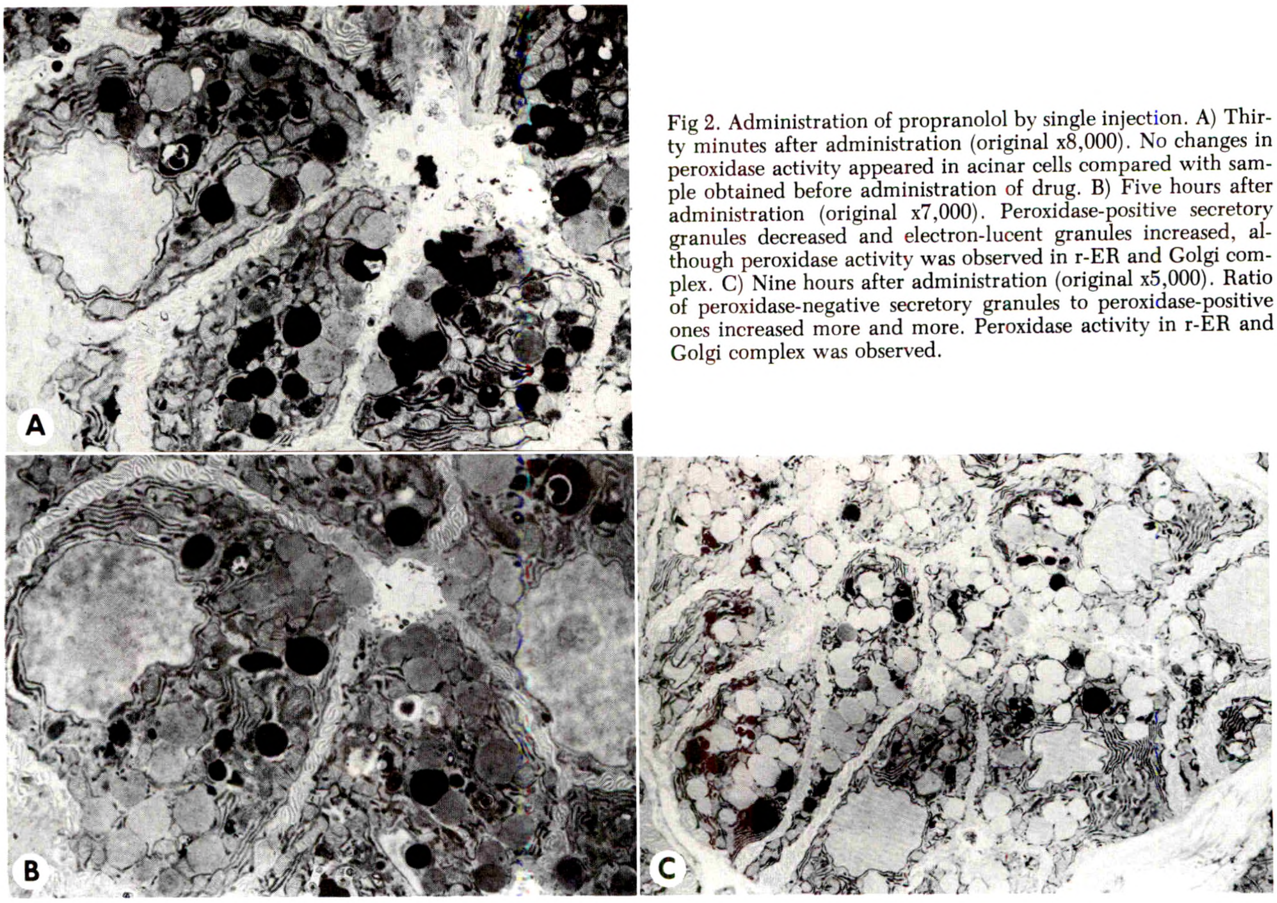

Fig 2. Administration of propranolol by single injection. A) Thirty minutes after administration (original x8,000). No changes in peroxidase activity appeared in acinar cells compared with sample obtained before administration of drug. B) Five hours after administration (original x7,000). Peroxidase-positive secretory granules decreased and electron-lucent granules increased, although peroxidase activity was observed in r-ER and Golgi complex. C) Nine hours after administration (original x5,000). Ratio of peroxidase-negative secretory granules to peroxidase-positive ones increased more and more. Peroxidase activity in r-ER and Golgi complex was observed.

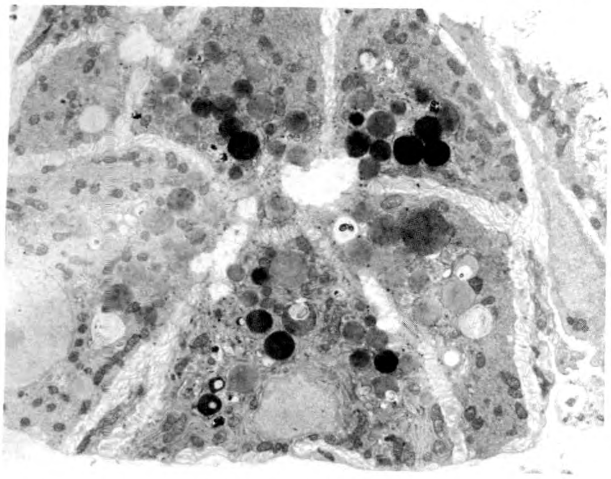

Fig 3. Continuous administration of propranolol over 7 hours (original x5,000). Very weak or no peroxidase activity was observed in r-ER and Golgi complex. In only small numbers of acinar cells was peroxidase activity observed in secretory granules.

observed in the secretory granules, but in these cells, no or only very little enzyme activity was observed in the r-ER. Many acinar cells had no peroxidase activity in any of the organelles.

ADMINISTRATION OF ISOPROTERENOL BY SINGLE INJECTION

Twenty Minutes After Administration (Fig 4A). The peroxidase reaction product was observed in every layer of the Golgi complex (inset). The reaction product in the secretory granules appeared in the form of dense granules that were discharged into the acinar lumen.

Sixty Minutes After Administration (Fig 4B). The lumen was enlarged and had an irregular border. The peroxidase reaction product was observed in the r-ER and Golgi complex. The electron-dense secretory granules decreased, and the size of the granules was variable. Some of the acinar cells displayed no secretory granules at all.

ADMINISTRATION OF ISOPROTERENOL AFTER INJECTION OF PROPRANOLOL (FIG 5)

The peroxidase reaction product was observed in the r-ER, Golgi complex, and secretory granules in acinar cells at 20 minutes and at 60 minutes after the intravenous injection. The distribution and enzyme activity of peroxidase in the acinar cells at both periods after the administration were the same as in those taken before the administration.

SAMPLES INCUBATED IN MEDIUM LACKING H_2O_2 AND CONTAINING 10^{-2} MOL/L POTASSIUM CYANIDE

The peroxidase reaction product was not observed in any acinar cells.

DISCUSSION

Vidian neurectomy[7] is an effective means of decreasing nasal secretion. After a neurectomy, the parasympathetic nerves innervating the nasal mucosa are blocked. It therefore is well established that secretion from nasal glands is stimulated by parasympathomimetic drugs. However, secretion induced by isoproterenol has up to now not been reported for nasal glands, though similar salivary secretion has been reported by many investigators.[8-11] It is thought that the volume of nasal secretion produced by the stimulation by isoproterenol is small compared with that produced by the stimulation from parasympathomimetic drugs.

When only β-blocker was administered, the peroxidase-positive secretory granules gradually decreased after the injection, although the reaction products were observed in the r-ER and Golgi complex. The electron-lucent secretory granules, which are thought to be formed by the stimulation of the parasympathetic nerve, gradually increased. It is known that secretion can occur in the absence of protein synthesis.[12,13] As the peroxidase-positive granules were secreted into the acinar lumen despite the absence of peroxidase synthesis, they scarcely were observed in the acinar cells after the

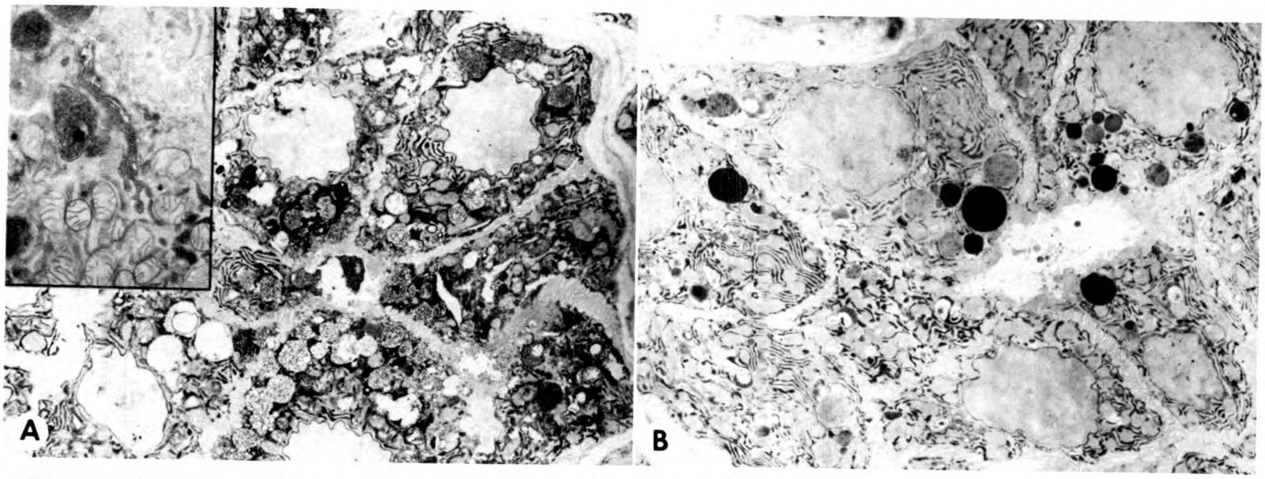

Fig 4. Administration of isoproterenol by single injection. A) Twenty minutes after administration (original x6,000). Peroxidase reaction product was observed in every layer of Golgi complex (inset [original x14,000]). Peroxidase was discharged into acinar lumen. B) Sixty minutes after administration (original x6,000). Lumen was enlarged. Peroxidase-positive granules decreased.

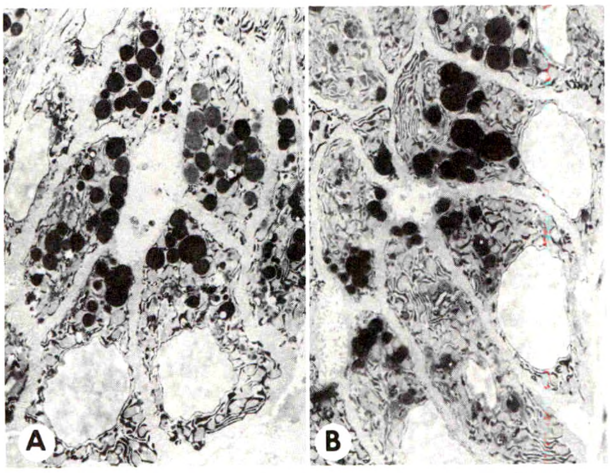

Fig 5. Administration of propranolol and isoproterenol (original x4,500). Distribution of peroxidase activity was same as in Fig 1. A) Twenty minutes after administration. B) Sixty minutes after administration.

injection of propranolol. It therefore is believed that only the peroxidase synthesis decreased after the administration of propranolol. A single intravenous injection of isoproterenol induces both the synthesis and the secretion of peroxidase at 20 minutes after the administration. If isoproterenol had induced not only the synthesis but also the secretion of peroxidase, peroxidase-positive granules would not have been observed when isoproterenol was injected after the administration of propranolol, since propranolol did not inhibit the secretion. Therefore, isoproterenol enhanced only the synthesis of peroxidase in the nasal glands in the same way that it does in the parotid gland.[10] As peroxidase was quickly synthesized by the injection of isoproterenol, peroxidase-positive granules were also quickly secreted, which made it appear that isoproterenol also enhanced secretion (Fig 4A). The appearance of small numbers of electron-dense secretory granules at 60 minutes after the administration of isoproterenol demonstrated that the rate of peroxidase synthesis had decreased after the secretion.

When propranolol was continuously injected over 7 hours, the peroxidase reaction product was not observed in the r-ER, and peroxidase-positive granules decreased. When propranolol was administered every day for 6 days, peroxidase activity disappeared in the r-ER and secretory granules of tracheal epithelial cells.[5] Continuous administration of propranolol for a long period of time also led to the disappearance of peroxidase activity in the r-ER of the acinar cells of the nasal glands. In our previous paper we observed that in the human nasal glands of a patient with a nasal allergy, peroxidase activity decreased in both the r-ER and secretory granules.[1] We therefore speculated that in the case of nasal allergy, the β-receptors around the nasal glands have been blocked or have received little stimulation for long periods.

It is concluded, therefore, that the synthesis of peroxidase in nasal glands is regulated by the stimulation through β-receptors. Though the role of peroxidase in nasal mucosa is unknown except for the virucidal and bactericidal actions, we can use the peroxidase in nasal glands as a marker for studying β-receptors in nasal mucosa.

It has been reported by other researchers that when stimulated by α-adrenergic and muscarinic cholinergic receptors, the parotid gland secretes water,[14,15] whereas in lacrimal glands the secretion of peroxidase was enhanced by stimulation with cholinergic[16] and α-adrenergic[17] but not β-adrenergic receptors. In our next report we intend to examine the responses of the nasal glands to α-adrenergic and cholinergic drugs.

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Ann Otol Rhinol Laryngol 99:1990

IMAGING CASE STUDY OF THE MONTH

TEMPORAL LOBE TUMOR MANIFESTED BY LOCALIZED DYSGEUSIA

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IOWA CITY, IOWA

CASE REPORT

A 54-year-old man presented with a 10-month history of chronic foul taste in the mouth localized to the upper left corner of the oral cavity. He stated that the sensation was sudden and bitter. He would abort this by drinking water or spitting, whereupon the symptoms would cease immediately. This would happen three to five times a day. There were no associated dental symptoms, halitosis, olfactory disturbance, or pain. He reported severe headaches over the past several years but only during winter months. He had seen numerous health care professionals, including dentists and an allergist, who were unable to help him.

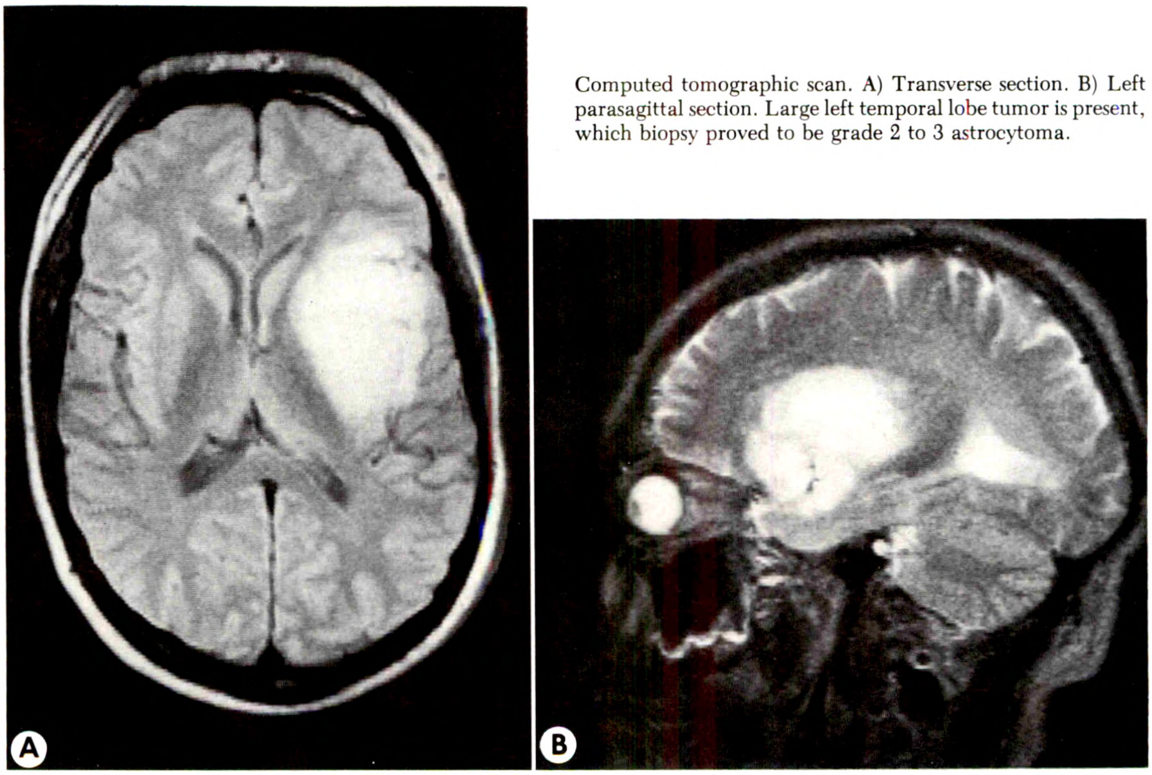
Findings on otolaryngic physical examination were normal. Gustation was present and equal on both sides of the anterior part of the tongue.

The patient developed a late complaint of perioral numbness, and even though this was unsubstantiated on neurologic examination, a brain computed tomograph was obtained. This revealed a large left temporal lobe tumor (see Figure). He underwent stereotaxic brain biopsy. The tissue report named a grade 2 to 3 astrocytoma. The patient underwent radiation therapy with nearly complete resolution of the symptom, which occurred only once per month.

DISCUSSION

Chronic dysgeusia is a symptom commonly seen by otolaryngologists. It is so common that if careful investigation of the oral cavity, salivary glands, and paranasal sinuses reveals no abnormalities, little further attention is paid to it in terms of serious disease. Generally, the dysgeusia is described by the patient as involving the whole mouth or tongue.

The patient's symptom was, of course, not due to an oral disturbance or disease process, but repre-



Computed tomographic scan. A) Transverse section. B) Left parasagittal section. Large left temporal lobe tumor is present, which biopsy proved to be grade 2 to 3 astrocytoma.

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sented gustatory hallucinations or complex partial seizures of the temporal lobe. Our neurologic and neurosurgical colleagues state this has been noted in their literature, but we cannot find it in our recent literature. We were not able to find mention of it in either of our two most modern and exhaustive texts in otolaryngology–head and neck surgery.[1,2] Hence, we feel it is worth pointing out.

It seems most likely that the best clue to pursuing this symptom as a brain tumor is its laterality and perhaps also its localization to a specific part of the oral cavity. Another clue would seem to be the patient's ability to abort the seizure immediately by oral manipulation such as drinking or spitting. Such a pattern should alert the otolaryngologist to the possibility of central nervous system disease.

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XX INTERNATIONAL CONGRESS OF AUDIOLOGY

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Ann Otol Rhinol Laryngol 99:1990

PATHOLOGY CONSULTATION

WARTHIN'S TUMOR

JOHN G. BATSAKIS, MD ADEL K. EL-NAGGAR, MD, PHD

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Warthin's tumor, classed as a monomorphic adenoma, ranks second to pleomorphic adenoma in the incidence of benign neoplasms of the parotid gland. By embryologic and clinicopathologic definitions, it is a neoplasm of the parotid gland and its environs, including parotid lymph nodes. Histopathologic diagnosis requires an oncocytic (mitochondria-rich) epithelium *and* lymphoid stroma. Malignant Warthin's tumors are rare and are carcinomas arising from the ductal component, or non-Hodgkin's lymphomas arising from the lymphoid tissue.

One of the first salivary gland tumors to be described, Warthin's tumor continues to fascinate clinicians, pathologists, and other investigators. Even its name has not been free of contention. For those who eschew eponyms, there have been at least 22 descriptive designations. Of these, papillary cystadenoma lymphomatosum is most widely accepted. If precedence in the literature is a consideration, the tumor should be named the Albrecht-Artz[1] tumor, since these authors' report antedates Warthin's[2] by 19 years. Expediency, however, favors the use of Warthin's tumor.

On the basis of embryologic studies of the migration and morphogenesis of the anlagen of the parotid gland and its relationship to developing lymphoid tissue and lymphoid nodes, a Warthin's tumor is anatomically restricted to the course of the anlagen and the final position of the parotid gland and its lymph nodes. The tumor, then, is a lesion of the parotid gland and environs, including the parotid lymph nodes.[3] Unacceptable, in that light, are "Warthin's tumors" in the submandibular gland and minor salivary tissues of the upper aerodigestive tracts — except for the labiobuccal area, in which they are rarely encountered. At all other sites, the masqueraders are only oncocytic hyperplasias in ductal epithelium associated with either a secondary chronic inflammation or indigenous lymphoid tissue, eg, nasopharynx, tonsil, or supraglottic larynx.[3]

Warthin's tumors characteristically occur in the superficial lobe of the parotid gland at or below the lower pole, eg, in a juxtaparotid lymph node. A sub-facial lobe location is less usual,[4] and the 13 of 125 Warthin's tumors said to have been found there by Lamelas et al[5] would seem to be a unique clinicopathologic experience. The number of intraparotid Warthin's tumors versus those arising in extraparotid lymph nodes cannot be gathered from the literature. Our personal experience indicates a 15:1 ratio in favor of the parotid location. Multicentricity can lead to a simultaneous involvement of both sites.[6]

As seen in the Table,[5,7-12] there is a considerable spread in the estimated incidence of the tumor. An even higher percentage, 20% to 30% of all parotid gland neoplasms, has been reported from Denmark.[13] Diligence of recording, the specialty character of the reporting institution, and inclusion of nonneoplastic diseases in the analyses may account for the differences. Data from salivary gland registries[7,8] are likely closest to the true incidence, with about 14% of all benign and malignant *epithelial* neoplasms of the parotid gland. This percentage is also in line with the usual experience of authors in private practice, eg, Lamelas et al[5] and Heller and Attie.[14] The latter report a 17% incidence in 929 benign parotid tumors they have personally treated.

The historical demographic depiction of Warthin's tumor as a salivary tumor of white men over the age of 40 has been challenged in the 1980s.[15,16] Since 1950, there has been a progressive change in gender statistics so that the earlier male to female ratio of 7:1 has now reportedly given way to a 1:1 ratio. If a selection bias is at work, the earlier data seem more vulnerable.[9-12]

Warthin's tumors are usually asymptomatic; only 10% of patients present with complaints other than a mass, most often at the angle of the mandible. Those complaints are pain, pressure sensations, or a rapid increase in size. Weakness of the facial nerve is rarely evident. There are, however, exceptions and these are related to rupture, iatrogenic or otherwise, of the cyst contents of the tumors. The histotoxicity and aseptic inflammation accompanying liberation of the Warthin's tumor fluid provide the signs and symptoms of an acute parotitis and even preoperative fistula with purulent drainage.

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INCIDENCE OF WARTHIN'S TUMOR

Author	*No. of Parotid Tumors*	*Warthin's Tumor (%)*
Eneroth[11]	2,158	4.7
Seifert et al[8]	2,779	14.4
Lamelas et al[5]	917	14.0
Foote and Frazell[10]	766	6.5
Beahrs et al[12]	760	5.4
McGurk et al[9]	673	5.0
Eveson and Cawson[7]	278	14.4

The more common absence of discomfort accounts for the relatively long duration before diagnosis: an average of 3 years and an average size of about 3.5 cm at discovery.[7]

The gross appearance of a Warthin's tumor is quite characteristic and can at times be diagnostic, especially if a pseudotubercular, cystic appearance is conveyed. Uncut, the circumscribed tumor is a brown to yellow-red cystic to moderately firm mass that ranges in size from 0.5 to 5.0 cm. Upon cutting, fluid escapes. The fluid's density and color varies from thin and yellow or brown and shimmering to thick and tenacious. The differences are caused by the amount of cellular and lipidic material and degree of inspissation. Formalin fixation accentuates the papillary configuration of the tumor.

Microscopically, an oncocytic epithelium having a tubulopapillary cystic architecture within lymphoid tissue or a lymph node is seen (see Figure, A). That within a lymph node has sinuses, an organized structure, and usually an embracing connective tissue capsule or connective tissue condensation.

Seifert et al[8] have, on the basis of examining 275 Warthin's tumors, histologically classified Warthin's tumors into four subtypes. Their classification is based primarily on the ratio of epithelium to the lymphoid stroma of the tumors. Subtype 1 or "typical" Warthin's tumor has an epithelial component of 50% of the tumor mass. Subtype 2 is stroma-poor, with an epithelial component of 70% to 80%. Seventy-five percent of their Warthin's tumors fell into subtype 1 and 90% of all the tumors were in types 1 and 2. Stroma-rich Warthin's tumors are those with an epithelial component of 20% to 30% and comprised 2% of the study group. These occurred only in men. Subtype 4 (metaplastic), comprising 7.5% of the tumors, are those Warthin's tumors with large areas of squamous metaplasia and regressive secondary changes (see Figure, B). Of interest is the observation that 20% of subtype 4 Warthin's tumors had been irradiated.

The subtype 1 Warthin's tumor is the one that comes readily to mind in the surgical-pathologic diagnosis of the lesion. The ratio of epithelium to lymphoid stroma is 1:1. Epithelial cells are in an irregular two-row alignment and possess acidophilic oncocytic cytoplasm. They protrude or form papillary projections into the lumens of macrocysts and microcysts. The basal-row cells are cuboidal, often pyramidal, in shape, in contrast to the taller cylindrical apical cells. These cells may show an apocrine secretion. Foci of squamous metaplasia, never extensive, and mucous goblet cells can be found. The contents of the cystic spaces are usually acidophilic — at times grumous and lipidic — and can contain desquamated epithelial cells, lymphoid cells, and crystalloids (see Figure, C).

The lymphoid stroma often contains reactive follicles and its cellular composition is usually that of a normal lymph node (see below).

In subtypes 1 and 2, areas of nonpapillary oncocytic proliferation are found. This tendency is much more pronounced in the stroma-poor type 2 Warthin's tumor and can suggest an oncocytoma.

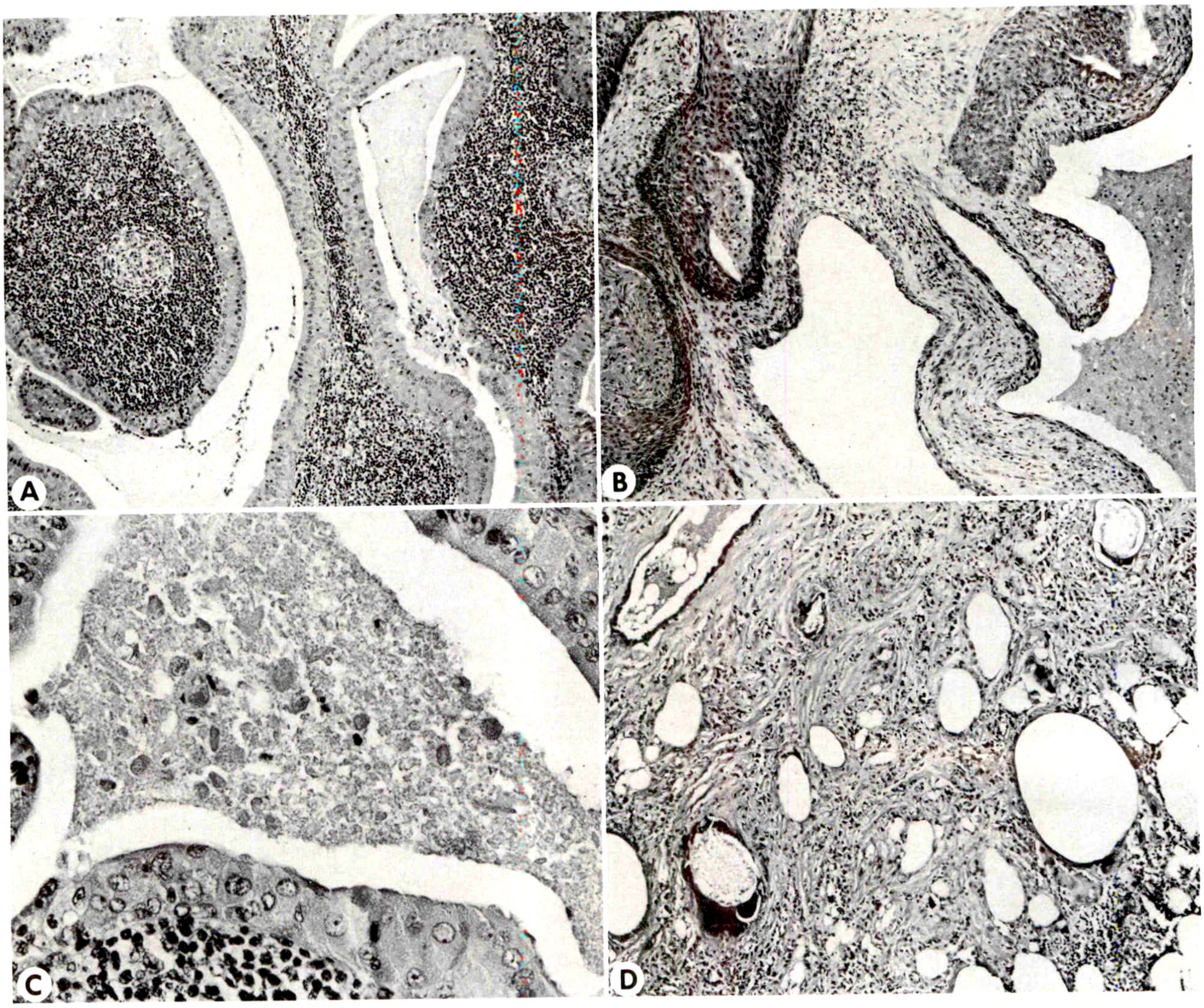
Subtypes 3 and 4 are characterized by a relative paucity of oncocytic cells. In the former, the lymphoid stroma dominates; in the latter an extensive squamous metaplasia, often accompanied by regressive changes, is characteristic. Oncocytic foci are few. Regressive changes consist of areas of hyalinization, liquefaction, and necrosis.

Regressive and inflammatory stromal changes are not limited to subtype 4. Granulomatous inflammation (lipid crystals, foreign body giant cells, xanthoma cells, histiocytes, macrophages) in response to the lipid-rich secretions of the cysts may be seen in any of the subtypes. The cyst contents can be extremely tissue-toxic and can on rare occasions be a cause for a sialocutaneous fistula.[13] Fine-needle aspiration of a Warthin's tumor can provoke a similar tissue reaction (see Figure, D). Ceroid pigment, considered by some to be an undegradable final product of lysosomal degradation of mitochondria, is often present in the macrophages of the lymphoid stroma.

A fifth type is also acknowledged, but diagnosis is conjectural since the tumor is necrotic or infarcted.

As may be expected, the epithelial (oncocyte) elements of Warthin's tumors exhibit a heterogeneity of keratin expression, with the cells on the luminal side coloring differently than cells on the basal side.[17,18] Immunohistochemical evidence does indicate that while any part of the salivary duct unit can give rise to the tumor, the striated and excretory ducts are sites of predilection.

The preponderance of immunologic and nonimmunologic histologic evidence does not support the premise that Warthin's tumor is a type of delayed hypersensitivity disease similar to Hashimoto's disease. Indeed, the highly organized structure of the lymphoid component, lack of circulating autoantibodies, and repeated affirmation of origin from enclaved salivary tissue within parotid and periparotid lymph nodes and lymphoid tissue should lay to rest the notion of an autoimmune basis.



Warthin's tumor of parotid gland. A) Showing required oncocytic epithelium, here arranged in papillae, and lymphoid tissue (H & E, original x65). B) Extensive squamous metaplasia of epithelium is accompanied by regressive changes in stroma (H & E, original x65). This change followed fine-needle aspiration biopsy. C) Cystic space is partially filled by grumous, lipid-rich material (H & E, original x200). D) Stromal tissue reaction to liberated tissue-toxic cyst contents (H & E, original x50). Clear spaces, some with foreign body giant cells at their margins, are lipid that has been removed by tissue preparation process.

The lymphoid component, however, continues to attract immunologic attention and in the event has yielded conflicting data.[19-22] Differences in various immunoglobulin classes and ratios of T to B cells given by authors can be ascribed to an inherent heterogeneity and also to the different techniques used to define these parameters. Two studies provide strong evidence that the lymphoid cells originate in constituents of a preexisting lymph node in most Warthin's tumors.[19,20] Howard et al[20] have demonstrated that the numbers of B and T lymphocytes are comparable to those of other lymph nodes. They also showed that a vigorous stimulatory response to phytohemagglutinin reflected a predominance of functional T cells. Caselitz et al[19] confirmed these findings by observing a clear and strong predominance of Leu 3a–positive T-helper cells. T-helper cells outnumbered T-suppressor cells by a factor of 4. Normal lymph nodes and peripheral blood are similar. In summary, the lymphoid stroma is a mainly follicular B-cell component with a polyclonal distribution of immunoglobulins and a mainly extrafollicular T-cell component in which T-helper cells predominate over T-suppressor (cytotoxic) cells.

Even though the lymphoid stroma of a Warthin's tumor may be an activated one, it is within the physiologic range of normal preexisting lymphoid tissues. Yamamoto et al[21] have indicated the subepithelial zone in the cystadenomas is a region of special cellular reaction (plasma cells, mast cells). In comparison to normal parotid gland, immunoglobulin E plasma cells are more numerous in Warthin's tumors — an effect that is not so obvious for the other immunoglobulin classes. Mast cells are found in greatest number in subepithelial areas, especially in epithelium-rich Warthin's tumors.

Multifocality is held responsible for the 5% to 25% "recurrence rates" reported for Warthin's tumors. Surgical management has included excisional biopsy, enucleation without removal of a margin of normal parotid tissue, subtotal parotidectomy, and total parotidectomy.[14] There are advocates for each and perhaps individualization of patients is the best approach. Probably the only indication for a local resection of a palpable tumor would be the Warthin's tumor occurring in a parotid lymph node in the neck away from the main gland itself.

Excluding the involvement by disseminated lymphomas, malignant lymphomas in Warthin's tumors are rare. They have been non-Hodgkin's and preponderantly low-grade.[23]

Equally rare is carcinoma in Warthin's tumors. For acceptance the carcinoma must arise *from* the epithelial elements of the Warthin's tumor, preferably manifesting transition zones between benign and malignant epithelium. Adherence to this definition excludes metastases to the lymphoid stroma and malignant neoplasms coincident with the Warthin's tumor. Seifert et al[24] found only one example in a series of 1,431 salivary gland tumors and later reported seven others from the literature.[8] Two of the eight were squamous carcinomas, two were undifferentiated carcinomas, and four were adenocarcinomas. Radiotherapy to the tumor was antecedent in both squamous cell carcinomas and one each of the adenocarcinomas and undifferentiated carcinomas. Six of the eight carcinomas have manifested metastases to regional lymph nodes. Distant metastases have also been recorded from one of the six. In the senior author's (J.G.B.) consultative service are four carcinomas arising in Warthin's tumors. Three are histologically low-grade adenocarcinomas and one is a histologically low-grade mucoepidermoid carcinoma. The rarity prompts early reporting, but the follow-up periods are too short for a statement on the biologic behavior of the carcinomas arising in Warthin's tumors.

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BOOK REVIEWS

Maxillofacial Trauma

Charles C. Alling III and Donald B. Osbon, editors. Hard cover, illustrated, indexed, 510 pages, 1988. Lea & Febiger, Philadelphia, Pa, $80.

This text provides a practical approach to the evaluation and management of maxillofacial trauma. The stated goal of this book is to provide basic and easy-to-read subject matter for residents and practitioners involved in repairing these injuries; this objective is definitely accomplished.

Emphasis is placed on mandibular fractures, fixation devices, and radiographic imaging, including an in-depth discussion of computed tomography. Other topics, such as cervical spine injuries, laryngeal trauma, and fronto-orbital-ethmoid fractures and associated complications, are covered in a briefer fashion. The surgical approaches and types of repair are covered sufficiently.

The illustrations and diagrams are instructive and clinically relevant. Those related to fracture diagnosis and repair are easy to understand and interpret. The majority of the references are taken from the oral surgical literature. This volume provides a solid foundation for the diagnosis and treatment of soft tissue and bony trauma of the facial skeleton. The clinically oriented information makes it a useful source of reference.

Joseph B. Jacobs, MD
New York, New York

Head and Neck Imaging

Galdino E. Valvassori, Richard A. Buckingham, Barbara L. Carter, William N. Hanafee, Mahmood F. Mafee. Hard cover, illustrated, indexed, 339 pages, 1988. Thieme Medical Publishers, New York, NY, $139.

The explosion of imaging technology has had enormous impact on visualization and understanding of head and neck anatomy in both healthy and disease states. In order to properly disseminate such information, a precise, reader-friendly, and current reference needs development. To this end, the authors of *Head and Neck Imaging* have clearly directed their efforts. This single-volume atlas and text is divided into four general areas that cover the temporal bone, the nose and paranasal sinuses, the oral cavity and related structures, and the hypopharynx and larynx.

Three-dimensional anatomy of normal temporal bones is presented effectively from the triad of computed tomographic (CT) sections, artists' renderings, and cadaver macrosection correlates. Other chapters exploit this scheme in evaluating congenital, inflammatory, neoplastic, and osseodystrophic lesions. Magnetic resonance imaging (MRI) of cerebellopontine angle disease, although now standard, is well reviewed. A point of misinformation on page 44 of this section should, however, be resolved. The value of the pediatric audiogram is well documented. The authors should delete the allegation that it is unreliable.

Current imaging technologies, such as CT-directed sialography and MRI surface coil systems for laryngeal lesions, have been highlighted for their diagnostic promise. The authors admittedly, however, note the persistent need for better techniques in determining the extent of soft tissue lesions, including adjacent structure involvement.

Overall, this work is well done and represents state-of-the-art information. Although cadaver macrosections would have enhanced chapters in addition to that on the temporal bone, the high-resolution studies presented in *Head and Neck Imaging* are of excellent quality and easily interpreted. This volume should prove a valuable reference for any practitioner of head and neck medicine and surgery.

Randolph A. McKenzie, MD
Dennis G. Pappas, MD
Birmingham, Alabama

Hearing Impairment in Children

Fred H. Bess, ed. Hard cover, illustrated, indexed, 450 pages, 1988. York Press, Parkton, Md, $55.

No matter what method of education and rehabilitation is employed, if hearing-impaired children are to recognize their full potential, a multidisciplinary approach must be used. This includes personal and family counseling, testing and evaluations, and medical and audiologic consultations and monitoring, along with other procedures. Every available technical aid, such as digital hearing aids, tactile instruments, cochlear implants, and classroom acoustic devices should be used to stimulate the development of speech.

Dr Bess presents papers from the Third International Symposium on Childhood Deafness that emphasize this philosophy in the management of hearing-impaired children. In a logical and methodical order, an excellent job has been done in reviewing many of the concerns unique to the management of a child with a sensorineural hearing loss.

The causes of auditory disorders, including genetic causes, infectious agents, syndromes, and high risk factors for hearing loss, are discussed in the first section. The second section addresses issues on the identification and assessment of hearing losses. The use of auditory brain stem response monitoring, behavioral audiometry, and acoustic immittance measurements is discussed, and information on hearing aid selection for the young child is provided.

Next follows a chapter on the assessment of the hearing-impaired child's communication skills. Of particular historical interest are the demographics of Dr Noel Matkin, who focuses on some of the deficiencies in providing services to infants and young children who are at risk for a sensorineural hearing loss. Ideally, comprehensive remedial services will be provided these children immediately upon identification of their hearing loss, and will be customized to accommodate their individual needs. Yet, too much time is still spent in identifying a hearing loss. Children with minimal or unilateral hearing losses are often identified late because of inadequate screenings, delayed medical intervention, and the lack of ongoing audiologic monitoring.

Management of hearing-impaired children's needs is covered in the third and final section of this text. Two of the chapters are devoted to management of their classroom needs. Several other chapters deal with management of their speech/language skills and other educational needs. Discussions on high-level amplifications, tactile hearing aids, and cochlear implants are provided. The chapter on hearing aids and their potential for producing hearing trauma is, by far, the best review of this topic to date. Earmold modifications to enhance the aided thresholds of severely and profoundly hearing-impaired children, and the option of digital hearing aids for those with mild to severe hearing loss are not included, however. The chapter on otitis media is timely. Unfortunately, the effect of otitis media or significant negative middle ear pressure on a child with a preexisting sensorineural hearing loss is not included. The last two chapters in this section speak to the ramifications of a child's hearing loss on others, especially parents. Useful ideas and advice are suggested for the professional who may be consulted for help.

It is the reviewers' belief that every hearing-impaired child is unique; not all can be oral, and not all can be total communicators. The method of communication should be chosen on the basis of individual needs and aptitudes. These thought-provoking papers should stimulate anyone involved in the education, habilitation, or speech and language development of hearing-impaired children. They should be of interest to physicians, audiologists, educators, and parents. Dr Bess has made a needed contribution to the management of the hearing-impaired child — an area that heretofore has been neglected in the literature.

Dennis G. Pappas, MD
Angela P. Naccari, MS
Birmingham, Alabama

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SPECIAL NOTE to Ms. JANE E. BRODY of The New York Times:
Here's further evidence that Spastic Dysphonia can be overcome by Direct Voice Rehabilitation.
—MORTON COOPER, Ph.D.

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September 9, 1989

TO WHOM IT MAY CONCERN:

In 1973, because of laryngitis and vocal misuse due to my career as Professor of Economics at the National University of Iran, my vocal chords gradually became weak in such a way that I could hardly speak.

In the beginning, I contacted an ear, nose and throat doctor in Tehran and he gave me antibiotics to use. I did not get better and in the summer of 1973 I went to England in order to see a voice therapist. This trip was of no use and my problem became worse.

In the summer of 1974, I went to the United States and consulted a cousin who, as a medical pathologist, was making research at Rutgers Medical School. She said that I should first see Dr. F. and, if his treatment might not be useful, I should go to Los Angeles to see Dr. Hans von Leden. Dr. F's prescription was funny as he told me to chew a golf ball and for this matter one of my teeth broke apart.

In Sept. of 1974, I went to see Dr. von Leden. He, for the first time, diagnosed my problem as Spastic Dysphonia and after extensive examinations referred me to Dr. Morton Cooper. Needless to say, before seeing Dr. von Leden, I went to see Dr. Shapoory, a nose, ear and throat specialist in Burbank. After different examinations, he also referred me to Dr. von Leden.

On Sept. 12, 1974, I saw Dr. Cooper. He said that I suffered from Spastic Dysphonia and should undergo vocal rehabilitation. The length of time needed for the treatment was stipulated as one to four years in the initial session, with the possibility that one year may be sufficient.

I stayed in Los Angeles from Sept. 1974 to July 1975. During this period, I used to see Dr. Cooper twice a week and in the beginning a few times a week. His treatment was a new experience in my life as I regained my natural voice and also my career.

In the beginning, I was pessimistic towards the outlook of the treatment, but after a few months, while exercising Dr. Cooper's methods and reading his book, I found out that my voice was going to its natural level without slipping back to a low level.

I still remember Dr. Cooper's statement, namely: "Since you are a theoretician and teach economic theory, you would be able to learn the right methods of speaking." This was proved, as his treatment became fully effective and, after 11 months, I was back to my real voice, without losing ends of words and sentences.

Personally, I owe my regained natural voice to Dr. Cooper. I admire his patience and kindness. Of course, I worked very hard during the period of rehabilitation, exercising his methods of humming words first and later sentences and breathing correctly.

Finally, I have been able to teach regularly every semester since Sept. 1975, carrying a full load of 15 hours per week on the average. Thanks to Dr. Cooper for his rehabilitation program.

Sincerely,

Fereydoon Tafazzol.

Fereydoon Tafazzoli, Ph.D.

Let's Hear Your Views!

Please send your comments on spastic dysphonia to MORTON COOPER, Ph.D., Suite 401, 10921 Wilshire Blvd., Los Angeles, CA 90024. He is the author of *Modern Techniques of Vocal Rehabilitation; Change Your Voice, Change Your Life; & Winning With Your Voice.*

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